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(54) Title: RENAL-SELECTIVE PRODRUGS FOR THE TREATMENT OF HYPERTENSION			
(57) Abstract <p>Renal-selective prodrugs are described which are preferentially converted in the kidney to compounds capable of inhibiting synthesis of catecholamine-type neurotransmitters involved in renal sympathetic nerve activity. The prodrugs described herein are derived from inhibitor compounds capable of inhibiting one or more of the enzymes involved in catecholamine synthesis, such compounds being classifiable as tyrosine hydroxylase inhibitors, or as depa-decarboxylase inhibitors, or as dopamine-β-hydroxylase inhibitors. These inhibitor compounds are linked to a chemical moiety, such as a glutamic acid derivative, by a cleavable bond which is recognized selectively by enzymes located predominantly in the kidney. The liberated inhibitor compound is then available in the kidney to inhibit one or more of the enzymes involved in catecholamine synthesis. Inhibition of renal catecholamine synthesis can suppress heightened renal nerve activity associated with sodium-retention related disorders such as hypertension. Conjugates of particular interest are glutamyl derivatives of dopamine-β-hydroxylase inhibitors, of which N-acetyl-Y-glutamyl fusaric acid is preferred.</p>			

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RENAL-SELECTIVE PRODRUGS FOR THE TREATMENT
OF HYPERTENSION

5

Related Application

This application is a continuation-in-part of U.S. Application Ser. No. 07/386,527 filed 27 July 1989.

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Field of the Invention

This invention is in the field of cardiovascular therapeutics and relates to a class of compounds useful in control of hypertension. Of particular interest is a class 15 of compounds which prevent or control hypertension by selective action on the renal sympathetic nervous system.

Background of the Invention

20 Hypertension has been linked to increased sympathetic nervous system activity stimulated through any of four mechanisms, namely (1) by increased vascular resistance, (2) by increased cardiac rate, stroke volume and output, (3) by vascular muscle defects or (4) by sodium 25 retention and renin release [J. P. Koepke et al, The Kidney in Hypertension, B. M. Brenner and J. H. Laragh (Editors), Vol. 1, p. 53 (1987)]. As to this fourth mechanism in particular, stimulation of the renal sympathetic nervous system can affect renal function and maintenance of 30 homeostasis. For example, an increase in efferent renal sympathetic nerve activity may cause increased renal vascular resistance, renin release and sodium retention [A. Zanchetti et al, Handbook of Hypertension, Vol. 8, Ch. 8, pp. 151-172 (1986)]. Such sympathetically mediated renal 35 vasoconstriction has been identified as an element in the

pathogenesis of early essential hypertension in man. [R. E. Katholi, Amer. J. Physiol., 245, F1-F14 (1983)].

Proper renal function is essential to

5. maintenance of homeostasis so as to avoid hypertensive conditions. Excretion of sodium is key to maintaining extracellular fluid volume, blood volume and ultimately the effects of these volumes on arterial pressure. Under steady-state conditions, arterial pressure rises to that

10 pressure level which will cause balance between urinary output and water/salt intake. If a perturbation in normal kidney function occurs causing renal sodium and water retention, as with sympathetic stimulation of the kidneys, arterial pressure will increase to a level to maintain

15 sodium output equal to intake. In hypertensive patients, the balance between sodium intake and output is achieved at the expense of an elevated arterial pressure.

During the early stages of genetically

20 spontaneous or desoxycorticosterone acetate-sodium chloride (DOCA-NaCl) induced hypertension in rats, a positive sodium balance has been observed to precede hypertension. Also, surgical sympathectomy of the kidneys has been shown to reverse the positive sodium balance and delay the onset of

25 hypertension [R. E. Katholi, Amer. J. Physiol., 245, F1-F14 (1983)]. Other chronic sodium retaining disorders are linked to heightened sympathetic nervous system stimulation of the kidneys. Congestive heart failure, cirrhosis and nephrosis are characterized by abnormal chronic sodium

30 retention leading to edema and ascites. These studies support the concept that renal selective pharmacological inhibition of heightened sympathetic nervous system activity to the kidneys may be an effective therapeutic treatment for chronic sodium-retaining disorders, such as

hypertension, congestive heart failure, cirrhosis, and nephrosis.

- One approach to reduce sympathetic nervous system effects on renal function is to inhibit the synthesis of one or more compounds involved as intermediates in the "catecholamine cascade", that is, the pathway involved in synthesis of the neurotransmitter norepinephrine. Stepwise, these catecholamines are synthesized in the following manner: (1) tyrosine is converted to dopa by the enzyme tyrosine hydroxylase; (2) dopa is converted to dopamine by the enzyme dopa decarboxylase; and (3) dopamine is converted to norepinephrine by the enzyme dopamine- β -hydroxylase.
- Inhibition of dopamine- β -hydroxylase activity, in particular, would increase the renal vasodilatory, diuretic and natriuretic effects due to dopamine. Inhibition of the action of any of these enzymes would decrease the renal vasoconstrictive, antidiuretic and antinatriuretic effects of norepinephrine. Therapeutically, these effects oppose chronic sodium retention.

- Many compounds are known to inhibit the action of the catecholamine-cascade-converting enzymes. For example, the compound α -methyltyrosine inhibits the action of the enzyme tyrosine hydroxylase. The compound α -methyldopa inhibits the action of the enzyme dopa-decarboxylase, and the compound fusaric acid inhibits the action of dopamine- β -hydroxylase. Such inhibitor compounds often cannot be administered systemically because of the adverse side effects induced by such compounds. For example, the desired therapeutic effects of dopamine- β -hydroxylase inhibitors, such as fusaric acid, may be offset by hypotension-induced compensatory stimulation of the

renin-angiotensin system and sympathetic nervous system, which promote sodium and water retention.

To avoid such systemic side effects, drugs may 5 be targetted to the kidney by creating a conjugate compound that would be a renal-specific prodrug containing the targetted drug modified with a chemical carrier moiety. Cleavage of the drug from the carrier moiety by enzymes predominantly localized in the kidney releases the drug in 10 the kidney. Gamma glutamyl transpeptidase and acylase are examples of such cleaving enzymes found in the kidney which have been used to cleave a targetted drug from its prodrug carrier within the kidney.

15 Renal targetted prodrugs are known for delivery of a drug selectively to the kidney. For example, the compound L- γ -glutamyl amide of dopamine when administered to dogs was reported to generate dopamine *in vivo* by specific enzymatic cleavage by γ -glutamyl transpeptidase 20 [J. J. Kyncl et al, Adv. Biosc., 20, 369-380 (1979)]. In another study, γ -glutamyl and N-acyl- γ -glutamyl derivatives of the anti-bacterial compound sulfamethoxazole were shown to deliver relatively high concentrations of sulfame- 25 thoxazole to the kidney which involved enzymatic cleavage of the prodrug by acylamino acid deacylase and γ -glutamyl transpeptidase [M. Orlowski et al, J. Pharmacol. Exp. Ther., 212, 167-172 (1980)]. The N- γ -glutamyl derivatives of 2-, 3-, or 4-aminophenol and p-fluoro-L-phenylalanine have been found to be readily solvolyzed *in vitro* by γ - 30 glutamyl transpeptidase [S.D.J. Magnan et al, J. Med. Chem., 25, 1018-1021 (1982)]. The hydralazine-like vasodilator 2-hydrazino-5-g-butylypyridine (which stimulates guanylate cyclase activity) when substituted with the N- acetyl- γ -glutamyl residue resulted in a prodrug which 35 provided selective renal vasodilation [K. G. Hofbauer et

al, J. Pharmacol. Exp. Ther., 212, 838-844 (1985)]. The dopamine prodrug γ -L-glutamyl-L-dopa ("gludopa") has been shown to be relatively specific for the kidney and to increase renal blood flow, glomerular filtration and 5 urinary sodium excretion in normal subjects [D. P. Worth et al, Clin. Sci. 69, 207-214 (1985)]. In another study, gludopa was reported to be an effective renal dopamine prodrug whose activity can be blocked by the dopa-decarboxylase inhibitor carbidopa [R. F. Jeffrey et al, Br. J. Clin. 10 Pharmac., 25, 195-201 (1988)].

BRIEF DESCRIPTION OF THE DRAWING FIGURES

15

Figure 1 shows the acute effects of i.v. injection of vehicle and Example #3 conjugate on mean arterial pressure in rats.

20

Figure 2 shows the acute effects of i.v. injection of vehicle and Example #3 conjugate on renal blood flow in rats.

25

Figure 3 shows the chronic effects of i.v. infusion of vehicle and Example #464 conjugate on mean arterial pressure in spontaneously hypertensive rats.

30

Figure 4 shows time-dependent formation of the dopamine- β -hydroxylase inhibitor fusaric acid from the Example #859 conjugate incubated with rat kidney homogenate.

Figure 5 shows time-dependent formation of fusaric acid from the Example #859 conjugate incubated with a mixture of purified acylase I and gamma-glutamyl transpeptidase at pH 7.4 and 8.1.

5

Figure 6 shows the concentration-dependent effect of fusaric acid and the Example #859 conjugate on norepinephrine production by dopamine- β -hydroxylase in vitro.

10

Figure 7 shows dopamine- β -hydroxylase inhibition in vitro by fusaric acid, the Example #859 conjugate and possible metabolites at a concentration of 20 μ M.

15

Figure 8 shows the acute effects of i.v. injection of fusaric acid and Example #859 conjugate on mean arterial pressure in spontaneously hypertensive rats.

20

Figure 9 shows the acute effects of i.v. injection of fusaric acid and Example #859 conjugate on renal blood flow in spontaneously hypertensive rats.

25

Figure 10 shows the effects of chronic i.v. infusion of vehicle, fusaric acid, and Example #859 conjugate for 5 days on mean arterial pressure in spontaneously hypertensive rats.

30

Figure 11 shows the effects of chronic i.v. infusion of vehicle and Example #863 conjugate for 4 days on mean arterial pressure in spontaneously hypertensive rats.

35

Figure 12 shows the heart tissue concentrations of norepinephrine following the 5 day infusion experiment described in Figure 10.

Figure 13 shows the kidney tissue concentrations of norepinephrine following the 5 day infusion experiment described in Figure 10.

5

Figure 14 shows the effects of Example #859 conjugate on mean arterial pressure in anesthetized dogs after i.v. injection at two doses.

10

Figure 15 shows the effects of Example #859 conjugate on renal blood flow in anesthetized dogs after i.v. injection at two doses.

15

DESCRIPTION OF THE INVENTION

Treatment of chronic hypertension or sodium-retaining disorders such as congestive heart failure, cirrhosis and nephrosis, may be accomplished by 20 administering to a susceptible or afflicted subject a therapeutically-effective amount of a renal-selective prodrug capable of causing selective blockage of heightened sympathetic nervous system effects on the kidney. An advantage of such renalselective prodrug therapy resides in 25 reduction or avoidance of adverse side effects associated with systemically-acting drugs.

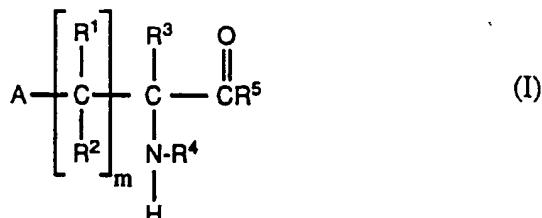
A renal-selective prodrug capable of providing renal sympathetic nerve blocking action may be provided by 30 a conjugate comprising a first residue and a second residue connected together by a cleavable bond. The first residue is derived from an inhibitor compound capable of inhibiting formation of a benzylhydroxyamine intermediate in the biosynthesis of an adrenergic neurotransmitter, and wherein 35 said second residue is capable of being cleaved from the

first residue by an enzyme located predominantly in the kidney.

The first and second residues are provided by
5 precursor compounds having suitable chemical moieties which react together to form a cleavable bond between the first and second residues. For example, the precursor compound of one of the residues will have a reactable carboxylic acid moiety and the precursor of the other residue will have a
10 reactable amino moiety or a moiety convertible to a reactable amino moiety, so that a cleavable bond may be formed between the carboxylic acid moiety and the amino moiety. An inhibitor compound which provides the first residue may be selected from tyrosine hydroxylase inhibitor
15 compounds, dopa-decarboxylase inhibitor compounds, dopamine- β -hydroxylase inhibitor compounds, and mimics of any of these inhibitor compounds.

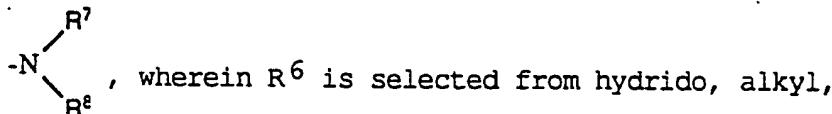
It is understood that the inhibitor compounds
20 described herein have been classified as tyrosine hydroxylase inhibitors, or as dopa-decarboxylase inhibitors, or as dopamine- β -hydroxylase inhibitors, for convenience of description. Some of the inhibitor compounds may be classifiable in more than one of these classes. For
25 example, 2-vinyl-3-phenyl-2-aminopropionic acid derivatives are classified herein as tyrosine hydroxylase inhibitors, but such derivatives may also act as dopa-decarboxylase inhibitors.

A class of compounds from which a suitable tyrosine hydroxylase inhibitor compound may be selected to provide the conjugate first residue is represented by Formula I:



5

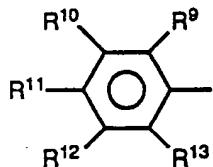
wherein each of R¹ through R³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl,
10 haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R⁴ selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein R⁵ is selected from -OR⁶ and
15



20

cycloalkyl, cycloalkylalkyl, aralkyl and aryl, and wherein each of R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein m is a number selected from zero through six:

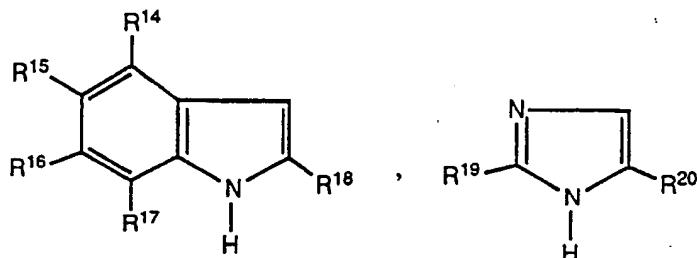
wherein A is a phenyl ring of the formula



- 5 wherein each of R⁹ through R¹³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl,
10 cycloalkenyl, alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy, formyl and a substituted or unsubstituted 5- or 6-membered heterocyclic ring selected from the group consisting of pyrrol-1-yl, 2-
15 carboxypyrrol-1-yl, imidazol-2-ylamino, indol-1-yl, carbozol-9-yl, 4,5-dihydro-4-hydroxy-4-trifluoromethylthiazol-3-yl, 4-trifluoromethylthiazol-2-yl, imidazol-2-yl and 4,5-dihydroimidazol-2-yl; wherein any two of the R⁹ through R¹³ groups may be taken together to form
20 a benzoheterocyclic ring selected from the group consisting of indolin-5-yl, 1-(N-benzoylcarbamimidoyl)indolin-5-yl, 1-carbamimidoylindolin-5-yl, 1H-2-oxindol-5-yl, insol-5-yl, 2-mercaptopbenzimidazol-5(6)-yl, 2-aminobenzimidazol-5-(6)-yl, 2-methanesulfonamidobenzimidazol-5(6)-yl, 1H-
25 benzoxanol-2-on-6-yl, 2aminobenzothiazol-6-yl, 2-amino-4-mercaptopbenzothiazol-6-yl, 2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-1,3-dimethyl-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 4-methyl-2(H) oxoquinolin-6-yl, quinoxalin-6-yl, 2-hydroxyquinoxalin-6-
30 6-yl, 2-hydroxquinoxalin-7-yl, 2,3-dihydroxyquinoxalin-6-yl and 2,3-didydro-3(4H)-oxo-1,4-benzoxazin-7-yl; 5-hydroxy-

4H-pyran-4-on-2-yl, 2-hydroxypyrid-4-yl, 2-aminopyrid-4-yl,
2-carboxypyrid-4-yl and tetrazolo-[1,5-a]pyrid-7-yl;
and wherein A may be selected from

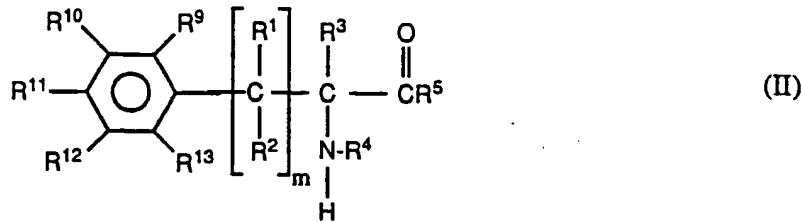
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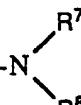
and $\begin{array}{c} R^{21} \\ | \\ -N \\ | \\ R^{22} \end{array}$,

- wherein each of R¹⁴ through R²⁰ is independently selected
from hydrido, alkyl, hydroxy, hydroxyalkyl, alkoxy,
cycloalkyl, cycloalkylalkyl, halo, haloalkyl, aryloxy,
10 alkoxycarboxyl, aryl, aralkyl, cyano, cyanoalkyl, amino,
monoalkylamino and dialkylamino, wherein each of R²¹ and
R²² is independently selected from hydrido, alkyl,
cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl,
alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxy carbonyl,
15 carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino,
alkylsulfinyl, alkylsulfonyl, arylsulfinyl and
arylsulfonyl; or a pharmaceutically-acceptable salt
thereof.

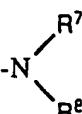
- 20 A preferred class of tyrosine hydroxylase
inhibitor compounds within Formula I is provided by
compounds of Formula II:



wherein each of R¹ and R² is hydrido; wherein m is one or two; wherein R³ is selected from alkyl, alkenyl and alkynyl; wherein R⁴ is selected from hydrido, alkyl,
5 cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein R⁵ is selected from -OR⁶ and

- 10  , wherein R⁶ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl and phenyl, and wherein each of R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, 15 alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R⁹ through R¹³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxycarbonyl, 20 alkoxycarbonyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, pyrrol-1-yl 2-carboxypyrrol-1-yl, imidazol-2-ylamino, indol-1-yl, 25 carbazol-9-yl, 4,5-dihydro-4-trifluoromethylthiazol-3-yl, 4-trifluoromethylthiazol-2-yl, imidazol-2-yl and 4,5-dihydroimidazol-2-yl, and wherein any two of the R⁹ through R¹³ groups may be taken together to form a benzoheterocyclic ring selected from the group consisting 30 of indolin-5-yl, 1-(N-benzoylcarbamimidoyl)indolin-5-yl, 1-carbamimidoylindolin-5-yl, 1H-2-oxindol-5-yl, indol-5-yl, 2-mercaptobenzimidazol-5(6)-yl, 2-aminobenzimidazol-5(6)-yl, 2-methanesulfonamidobenzimidazol-5(6)-yl, 1H-

benzoxanol-2-on-6-yl, 2-amino-benzothiazol-6-yl, 2-amino-4-mercaptopbenzothiazol-6-yl, 2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-1,3-dimethyl-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 4-methyl-2(H)-oxoquinolin-6-yl, quinoxalin-6-yl, 2-hydroxyquinoxalin-6-yl, 2-hydroxquinoxalin-7-yl, 2,3-dihydroxyquinoxalin-6-yl and 2,3-dihydro-3(4H)-oxo-1,4-benzoxazin-7-yl; wherein R³ is -CH=CH² or -C≡CH; wherein R⁵ is selected from -OR⁶ and

10  , wherein R⁶ is selected from

hydrido, alkyl, hydroxy, hydroxyalkyl, alkoxy, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino; and wherein each of R⁷ and R⁸ independently is selected from hydrido, alkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; or a pharmaceutically-acceptable salt thereof.

A first sub-class of preferred tyrosine hydroxylase inhibitor compounds consists of the following specific compounds within Formula II:

20 4-cyanoamino- α -methylphenylalanine;
 3-carboxy- α -methylphenylalanine;
 3-cyano- α -methylphenylalanine methyl ester;
 α -methyl-4-thiocarbamoylphenylalanine methyl ester;

25 4-(aminomethyl)- α -methylphenylalanine;
 4-guanidino- α -methylphenylalanine;
 3-hydroxy-4-methanesulfonamido- α -methylphenylalanine;
 3-hydroxy-4-nitro- α -methylphenylalanine;
 4-amino-3-methanesulfonyloxy- α -methylphenylalanine;

30 3-carboxymethoxy-4-nitro- α -methylphenylalanine;
 α -methyl-4-amino-3-nitrophenylalanine;
 3,4-diamino- α -methylphenylalanine;
 α -methyl-4-(pyrrol-1-yl)phenylalanine;

- 4-(2-aminoimidazol-1-yl)- α -methylphenylalanine;
- 4-(imidazol-2-ylamino)- α -methylphenylalanine;
- 4-(4,5-dihydro-4-hydroxy-4-trifluoromethyl-thiazol-2-yl)- α -methylphenylalanine methyl ester;
- 5 α -methyl-4-(4-trifluoromethylthiazol-2-yl)phenylalanine;
 α -methyl-3-(4-trifluoromethylthiazol-2-yl)-phenylalanine;
4-(imidazol-2-yl)- α -methylphenylalanine;
4-(4,5-dihydroimidazol-2-yl)- α -methylphenylalanine;
3-(imidazol-2-yl)- α -methylphenylalanine;
- 10 3-(4,5-dihydroimidazol-2-yl)- α -methylphenylalanine;
4-(imidazol-2-yl)phenylalanine;
4,5-dihydroimidazol-2-yl)phenylalanine;
3-(imidazol-2-yl)phenylalanine;
3-(2,3-dihydro-1H-indol-4-yl)- α -methylalanine;
- 15 α -methyl-3-(1H-2-oxindol-5-yl)alanine;
3-[1-(N-benzoylcarbamimidoyl)-2,3-dihydro-1H-indol-5-yl]- α -methylalanine;
3-(1-carbamimidoyl-2,3-dihydro-1H-indol-5-yl)- α -methylalanine;
- 20 3-(1H-indol-5-yl)- α -methylalanine;
3-(benzimidazol-2-thione-5-yl)- α -methylalanine;
3-(2-aminobenzimidazol-5-yl)-2-methylalanine;
2-methyl-3-(benzoxazol-2-on-6-yl)alanine;
3-(2-aminobenzothiazol-6-yl)-2-methylalanine;
- 25 3-(2-amino-4-mercaptopbenzothiazol-6-yl)-2methylalanine;
3-(2-aminobenzothiazol-6-yl)alanine;
2-methyl-3-(2,1,3-benzothiadiazol-5-yl)alanine;
3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)-2methylalanine-2,2-dioxide;
- 30 3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)-2-methylalanine-2,2-dioxide methyl ester;
3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)alanine 2,2-dioxide;
3-(1,3-dihydro-1,3-dimethylbenzo-2,1,3-thiadiazol-5y1)-2-methylalanine 2,2-dioxide;
- 35 3-(1,3-dihydro-1,3-dimethylbenzo-2,1,3-thiadiazol-5y1)-2-methylalanine 2,2-dioxide;

- α -methyl-3-[4-methyl-2(1H)-oxoquinolin-6-yl]alanine;
3-[4-methyl-2(1H)-oxoquinolin-6-yl]alanine;
2-methyl-3-(quinoxalin-6-yl)alanine;
2-methyl-3-(2-hydroxyquinoxalin-6-yl)alanine;
5 2-methyl-3-(2-hydroxyquinoxalin-7-yl)alanine;
3-(2,3-dihydroxyquinoxalin-6-yl)-2-methylalanine;
3-(quinoxalin-6-yl)alanine;
3-(2,3-dihydroxyquinoxalin-6-yl)alanine;
3-(1,4-benzoxazin-3-one-6-yl)-2-methylalanine;
10 3-(1,4-benzoxazin-3-one-7-yl)alanine;
3-(5-hydroxy-4H-pyran-4-on-2-yl)-2-methylalanine;
3-(2-hydroxy-4-pyridyl)-2-methylalanine;
3-(2-carboxy-4-pyridyl)-2-methylamine;
 α -methyl-4-(pyrrol-1-yl)phenylalanine;
15 α -ethyl-4-(pyrrol-1-yl)phenylalanine;
 α -propyl-4-(pyrrol-1-yl)phenylalanine;
4-[2-(carboxy)pyrrol-1-yl]phenylalanine;
 α -methyl-4-(pyrrol-1-yl)phenylalanine;
3-hydroxy- α -4-(pyrrol-1-yl)phenylalanine;
20 3-methoxy- α -4-(pyrrol-1-yl)phenylalanine;
4-methoxy- α -3-(pyrrol-1-yl)phenylalanine;
4-(indol-1-yl)- α -methylphenylalanine;
4-(carbazol-9-yl)- α -methylphenylalanine;
2-methyl-3-(2-methanesulfonylamidobenzimidazol-5-
25 yl)alanine;
2-methyl-3-(2-amino-4-pyridyl)alanine;
2-methyl-3[tetrazolo-(1,5)- α -pyrid-7-yl]alanine;
D,L- α - β -(4-hydroxy-3-methyl)phenylalanine;
D,L- α - β -(4-hydroxy-3-phenyl)phenylalanine;
30 D,L- α - β -(4-hydroxy-3-benzyl)phenylalanine;
D,L- α - β -(4-methoxy-3-cyclohexyl)phenylalanine;
 α , β , β trimethyl- β -(3,4-dihydroxyphenyl)alanine;
 α , β , β trimethyl- β -(4-hydroxyphenyl)alanine;
N-methyl α , β , β trimethyl- β -(3,4-dihydroxyphenyl)alanine;
35 D,L α , β , β trimethyl- β -(3,4-dihydroxyphenyl)alanine;

trimethyl- β - (3,4-dimethoxyphenyl)alanine;
L- α -methyl- β -3,4-dihydroxyphenylalanine;
L- α -ethyl- β -3,4-dihydroxyphenylalanine;
L- α -propyl- β -3,4-dihydroxyphenylalanine;
5 L- α -butyl- β -3,4-dihydroxyphenylalanine;
L- α -methyl- β -2,3-dihydroxyphenylalanine;
L- α -ethyl- β -2,3-dihydroxyphenylalanine;
L- α -propyl- β -2,3-dihydroxyphenylalanine;
L- α -butyl- β -2,3-dihydroxyphenylalanine;
10 L- α -methyl-4-chloro-2,3-dihydroxyphenylalanine;
L- α -ethyl-4-chloro-2,3-dihydroxyphenylalanine;
L- α -propyl-4-chloro-2,3-dihydroxyphenylalanine;
L- α -butyl-4-chloro-2,3-dihydroxyphenylalanine;
L- α -ethyl- β -4-methyl-2,3-dihydroxyphenylalanine;
15 L- α -methyl- β -4-methyl-2,3-dihydroxyphenylalanine;
L- α -propyl- β -4-methyl-2,3-dihydroxyphenylalanine;
L- α -butyl- β -4-methyl-2,3-dihydroxyphenylalanine;
L- α -methyl- β -4-fluoro-2,3-dihydroxyphenylalanine;
L- α -ethyl- β -4-fluoro-2,3-dihydroxyphenylalanine;
20 L- α -propyl- β -4-fluoro-2,3-dihydroxyphenylalanine;
L- α -butyl- β -4-fluoro-2,3-dihydroxyphenylalanine;
L- α -methyl- β -4-trifluoromethyl-2,3-dihydroxyphenylalanine
L- α -ethyl- β -4-trifluoromethyl-2,3-dihydroxyphenylalanine
L- α -propyl- β -4-trifluoromethyl-2,3-dihydroxyphenylalanine
25 L- α -butyl- β -4-trifluoromethyl-2,3-dihydroxyphenylalanine
L- α -methyl- β -3,5-dihydroxyphenylalanine;
L- α -ethyl- β -3,5-dihydroxyphenylalanine;
L- α -propyl- β -3,5-dihydroxyphenylalanine;
L- α -butyl- β -3,5-dihydroxyphenylalanine;
30 L- α -methyl- β -4-chloro-3,5-dihydroxyphenylalanine;
L- α -ethyl- β -4-chloro-3,5-dihydroxyphenylalanine;
L- α -propyl- β -4-chloro-3,5-dihydroxyphenylalanine;
L- α -butyl- β -4-chloro-3,5-dihydroxyphenylalanine;
L- α -methyl- β -4-fluoro-3,5-dihydroxyphenylalanine;
35 L- α -ethyl- β -4-fluoro-3,5-dihydroxyphenylalanine;

- L- α -propyl- β -4-fluoro-3,5-dihydroxyphenylalanine;
L- α -butyl- β -4-fluoro-3,5-dihydroxyphenylalanine
L- α -methyl- β -4-trifluoromethyl-3,5-dihydroxyphenylalanine;
L- α -ethyl- β -4-trifluoromethyl-3,5-dihydroxyphenylalanine;
5 L- α -propyl- β -4-trifluoromethyl-3,5-dihydroxyphenylalanine;
L- α -butyl- α -4-trifluoromethyl-3,5-dihydroxyphenylalanine;
L- α -methyl-2,5-dihydroxyphenylalanine;
L- α -ethyl-2,5-dihydroxyphenylalanine;
L- α -propyl-2,5-dihydroxyphenylalanine;
10 L- α -butyl-2,5-dihydroxyphenylalanine;
L- α -methyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -ethyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -propyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -butyl- β -4-chloro-2,5-dihydroxyphenylalanine;
15 L- α -methyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -ethyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -propyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -butyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -methyl- β -methyl-2,5-dihydroxyphenylalanine;
20 L- α -ethyl- β -methyl-2,5-dihydroxyphenylalanine;
L- α -propyl- β -methyl-2,5-dihydroxyphenylalanine;
L- α -butyl- β -methyl-2,5-dihydroxyphenylalanine;
L- α -methyl- β -4-trifluoromethyl-2,5-dihydroxyphenylalanine;
L- α -ethyl- β -4-trifluoromethyl-2,5-dihydroxyphenylalanine;
25 L- α -propyl- β -4-trifluoromethyl-2,5-dihydroxyphenylalanine;
L- α -butyl- β -4-trifluoromethyl-2,5-dihydroxyphenylalanine;
L- α -methyl- β -3,4,5-trihydroxyphenylalanine;
L- α -ethyl- β -3,4,5-trihydroxyphenylalanine;
L- α -propyl- β -3,4,5-trihydroxyphenylalanine;
30 L- α -butyl- β -3,4,5-trihydroxyphenylalanine;
L- α -methyl- β -2,3,4-trihydroxyphenylalanine;
L- α -ethyl- β -2,3,4-trihydroxyphenylalanine;
L- α -propyl- β -2,3,4-trihydroxyphenylalanine;
L- α -butyl- β -2,3,4-trihydroxyphenylalanine;
35 L- α -methyl- β -2,4,5-trihydroxyphenylalanine;

- L- α -ethyl- β -2,4,5-trihydroxyphenylalanine;
L- α -propyl- β -2,4,5-trihydroxyphenylalanine;
L- α -butyl- β -2,4,5-trihydroxyphenylalanine;
L-phenylalanine;
- 5 D,L- α -methylphenylalanine;
D,L-3-iodophenylalanine;
D,L-3-iodo- α -methylphenylalanine;
3-iodotyrosine;
3,5-diiodotyrosine;
- 10 L- α -methylphenylalanine;
D,L- α - β -(4-hydroxy-3-methylphenyl)alanine;
D,L- α - β -(4-methoxy-3-benzylphenyl)alanine;
D,L- α - β -(4-hydroxy-3-benzylphenyl)alanine;
D,L- α - β -(4-methoxy-3-cyclohexylphenyl)alanine;
- 15 D,L- α - β -(4-hydroxy-3-cyclohexylphenyl)alanine;
D,L- α - β -(4-methoxy-3-methylphenyl)alanine;
D,L- α - β -(4-hydroxy-3-methylphenyl)alanine;
N,O-dibenzylloxycarbonyl-D,L- α - β -(4-hydroxy-3-methylphenyl)alanine;
- 20 N,O-dibenzylloxycarbonyl-D,L- α - β -(4-hydroxy-3-methylphenyl)alanine amide;
D,L- α - β -(4-hydroxy-3-methylphenyl)alanine amide;
N,O-diacetyl-D,L- α - β -(4-hydroxy-3-methylphenyl)alanine;
D,L-N-acetyl- α - β -(4-hydroxy-3-methylphenyl)alanine;
- 25 L-3,4-dihydroxy- α -methylphenylalanine;
L-4-hydroxy-3-methoxy- α -methylphenylalanine;
L-3,4-methylene-dioxy- α -methylphenylalanine;
2-vinyl-2-amino-3-(2-methoxyphenyl)propionic acid;
2-vinyl-2-amino-3-(2,5-dimethoxyphenyl)propionic acid;
- 30 2-vinyl-2-amino-3-(2-imidazolyl)propionic acid;
2-vinyl-2-amino-3-(2-methoxyphenyl)propionic acid ethyl ester;
 α -methyl- β -(2,5-dimethoxyphenyl)alanine;
 α -methyl- β -(2,5-dihydroxyphenyl)alanine;
- 35 α -ethyl- β -(2,5-dimethoxyphenyl)alanine;

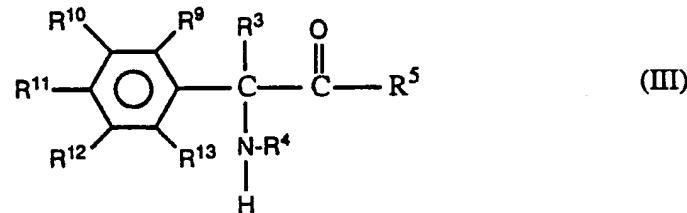
- α -ethyl- β -(2,5-dihydroxyphenyl)alanine;
- α -methyl- β -(2,4-dimethoxyphenyl)alanine;
- α -methyl- β -(2,4-dihydroxyphenyl)alanine;
- α -ethyl- β -(2,4-dimethoxyphenyl)alanine;
- 5 5 α -ethyl- β -(2,4-dihydroxyphenyl)alanine;
- α -methyl- β -(2,5-dimethoxyphenyl)alanine ethyl ester;
- 2-ethynyl-2-amino-3-(3-indolyl)propionic acid;
- 2-ethynyl-2,3-(2-methoxyphenyl)propionic acid;
- 2-ethynyl-2,3-(5-hydroxyindol-3-yl)propionic acid;
- 10 10 2-ethynyl-2-amino-3-(2,5-dimethoxyphenyl)propionic acid;
- 2-ethynyl-2-amino-3-(2-imidazolyl)propionic acid;
- 2-ethynyl-2-amino-3-(2-methoxyphenyl)propionic acid ethyl ester;
- 3-carbomethoxy-3-(4-benzyloxybenzyl)-3-aminoprop-1-yne;
- 15 15 α -ethynyltyrosine hydrochloride;
- α -ethynyltyrosine;
- α -ethynyl-m-tyrosine;
- α -ethynyl- β -(2-methoxyphenyl)alanine;
- α -ethynyl- β -(2,5-dimethoxyphenyl)alanine; and
- 20 20 α -ethynylhistidine.

A second sub-class of preferred tyrosine hydroxylase inhibitor compounds consists of compounds wherein at least one of R¹⁰, R¹¹ and R¹² is selected from hydroxy, alkoxy, aryloxy, aralkoxy and alkoxy carbonyl. More preferred compounds of this second sub-class are

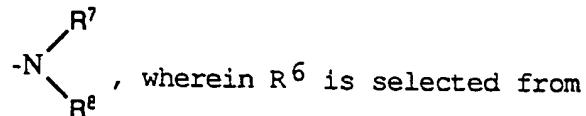
- 25 α -methyl-3-(pyrrol-1-yl)tyrosine;
- α -methyl-3-(4-trifluoromethylthiazol-2-yl)tyrosine;
- 3-(imidazol-2-yl)- α -methyltyrosine;
- 30 30 L- α -m-tyrosine;
- L- α -ethyl-m-tyrosine;
- L- α -propyl-m-tyrosine;
- L- α -butyl-m-tyrosine;
- L- α -p-chloro-m-tyrosine;
- 35 35 L- α -ethyl-p-chloro-m-tyrosine;

- L- α -butyl-p-chloro-m-tyrosine;
L α -p-bromo-m-tyrosine;
L- α -ethyl-p-bromo-m-tyrosine;
L- α -butyl-p-bromo-m-tyrosine;
5 L α -p-fluoro-m-tyrosine;
L α -p-iodo-m-tyrosine;
L- α -ethyl-p-iodo-m-tyrosine;
L α -p-methyl-m-tyrosine;
L α -p-ethyl-m-tyrosine;
10 L- α -ethyl-p-ethyl-m-tyrosine;
L- α -ethyl-p-methyl-m-tyrosine;
L α -p-butyl-m-tyrosine;
L α -p-trifluoromethyl-m-tyrosine;
L-3-iodotyrosine;
15 L-3-chlorotyrosine;
L-3,5-diiodotyrosine;
L- α -methyltyrosine;
D,L- α -methyltyrosine;
D,L-3-iodo- α -methyltyrosine;
20 L-3-bromo- α -methyltyrosine;
D,L-3-bromo- α -methyltyrosine;
L-3-chloro- α -methyltyrosine;
D,L-3-chloro- α -methyltyrosine; and
2-vinyl-2-amino-3-(4-hydroxyphenyl)propionic acid.
- 25

Another preferred class of tyrosine hydroxylase inhibitor compounds within Formula I consists of compounds



wherein R³ is selected from alkyl, alkenyl and alkynyl; wherein R⁴ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein m is a number selected from zero through five, inclusive; wherein R⁵ is selected from OR⁶ and

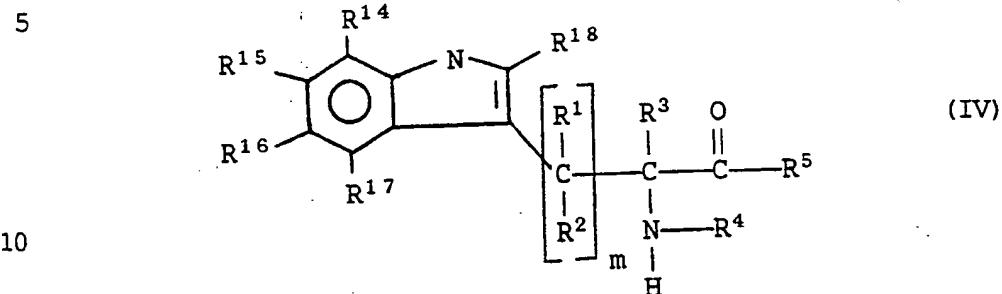


- 10 hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl and phenyl, and wherein each of R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino,
- 15 monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R⁹ through R¹³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxycarbonyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl,
- 20 alkoxycarbonyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

A preferred sub-class of compounds within

- 25 Formula III consists of compounds wherein at least one of R¹⁰, R¹¹ and R¹² is selected from hydroxy, alkoxy, aryloxy, aralkoxy and alkoxycarbonyl. More preferred compounds of this sub-class are methyl (+)-2-(4-hydroxyphenyl)glycinate; isopropyl and 3-methyl butyl esters of (+)-2-(4-
- 30 hydroxyphenyl)glycine; (+)-2-(4-hydroxyphenyl)glycine; (-)-2-(4-hydroxyphenyl)glycine; (+)-2-(4-methoxyphenyl)-glycine; and (+)-2-(4-hydroxyphenyl)glycinamide.

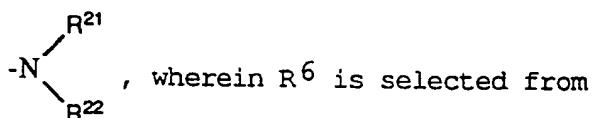
Still another preferred class of tyrosine hydroxylase inhibitor compounds within Formula I is provided by compounds of Formula IV:



wherein each of R^1 and R^2 is hydrido; wherein m is a number selected from zero through five, inclusive; wherein R^3 is selected from alkyl, alkenyl and alkynyl; wherein R^4 is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R^{14} through R^{17} is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy and formyl.

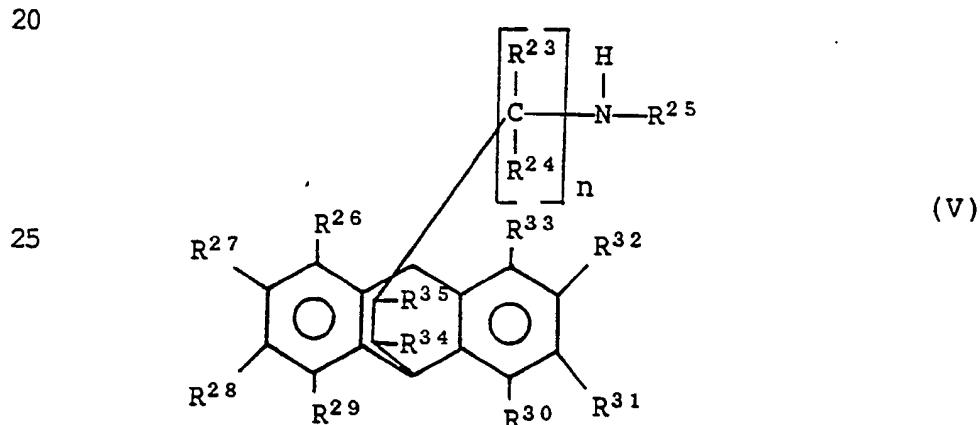
A preferred sub-class of compounds within Formula IV consists of L- α -methyltryptophan; D,L-5-methyltryptophan; D,L-5-chlorotryptophan; D,L-5-bromotryptophan; D,L-5-iodotryptophan; L-5-hydroxytryptophan; D,L-5-hydroxy- α -methyltryptophan; α -ethynyltryptophan; 5-methoxymethoxy- α -ethynyltryptophan; and 5-hydroxy- α -ethynyltryptophan.

Still another preferred class of tyrosine hydroxylase inhibitor compounds within Formula I is provided by compounds wherein A is



three, inclusive. More preferred compounds in this class are 2-vinyl-2-amino-5-aminopentanoic acid and 2-ethynyl-2-amino-5-aminopentanoic acid.

Still another preferred class of tyrosine hydroxylase inhibitor compounds within Formula I is provided by compounds of Formula V:



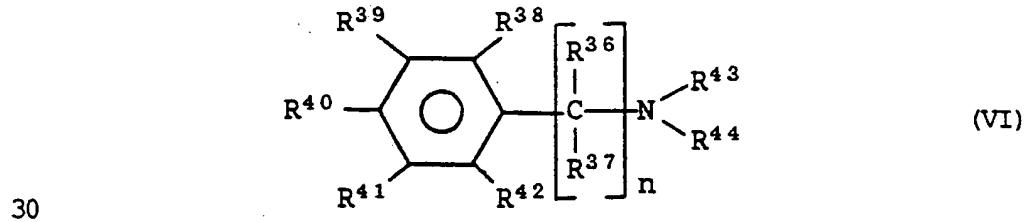
wherein each of R²³ and R²⁴ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl,

haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R²⁵ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, 5 haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R²⁶ through R³⁵ is independently selected from hydrido, hydroxy, alkyl, 10 cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl, aminomethyl, 15 alkylsulfanamido, nitro, alkylsulfonyloxy, alkoxy and formyl; wherein n is a number selected from zero through five, inclusive; or a pharmaceutically-acceptable salt thereof. A more preferred compound of this class is benzoctamine.

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A class of compounds from which a suitable dopa-decarboxylase inhibitor compound may be selected to provide the conjugate first residue is represented by Formula VI:

25



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wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, 35 aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl,

hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy,

5 carboxyalkoxy and formyl; wherein n is a number from zero through four; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino,

10 monoalkylamino, dialkylamino, monoalkylcarbonylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, alkenyl, cycloalkenyl and alkynyl, wherein any R⁴³ and R⁴⁴ substituent having a substitutable position may be further substituted with one or more groups selected from

15 hydroxyalkyl, halo, haloalkyl, carboxyl, alkoxyalkyl, alkoxycarbonyl; with the proviso that R⁴³ and R⁴⁴ cannot both be carboxyl at the same time, and with the further proviso that at least one of R⁴³ through R⁴⁴ is a primary or secondary amino group; or a pharmaceutically-acceptable

20 salt thereof.

A preferred class of compounds within Formula VI consists of compounds wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl;

25 wherein n is a number from one through three; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl, amino, mono-

30 alkylamino, dialkylamino, carboxyl, carboxyalkyl and alkanoyl; and wherein any R⁴³ and R⁴⁴ substituent having a

35

substitutable position may be further substituted with one or more groups selected from hydroxyalkyl, halo, haloalkyl, carboxyl, alkoxyalkyl, alkoxycarbonyl.

- 5 A more preferred class of compounds within Formula VI consists of those compounds wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, benzyl, phenyl, alkoxy, benzyloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, amino, 10 monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, cyanoamino, cyano, aminomethyl, carboxyl, carboxyalkoxy and formyl; wherein n is one or two; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, benzyl, phenyl, alkoxyalkyl, haloalkyl, 15 hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl and alkanoyl; and wherein any R⁴³ and R⁴⁴ substituent having a substitutable position may be further substituted with one or more groups selected from hydroxyalkyl, halo, haloalkyl, carboxyl, alkoxyalkyl, 20 alkoxycarbonyl.

- An even more preferred class of compounds within Formula VI consists of those compounds wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl, aminomethyl, carboxyalkoxy and formyl; wherein n is one or two; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, 25 carboxyl and carboxyalkyl; and wherein any R⁴³ and R⁴⁴ substituent having a substitutable position may be further substituted with one or more groups selected from hydroxyalkyl, halo, haloalkyl, carboxyl, alkoxyalkyl, alkoxycarbonyl.

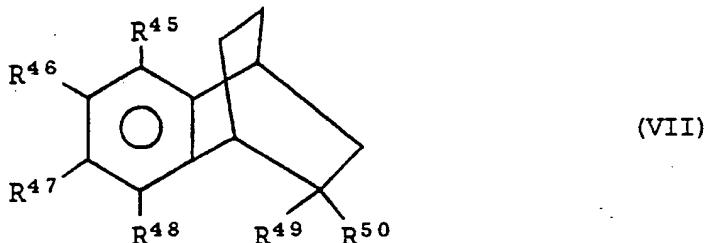
A more highly preferred class of compounds within Formula VI consists of those compounds wherein each of R³⁶ and R³⁷ is hydrido and n is one; wherein each of R³⁸ through R⁴² is independently selected from hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl and carboxyalkyl; and wherein any R⁴³ and R⁴⁴ substituent having a substitutable position may be further substituted with one or more groups selected from hydroxyalkyl, halo, haloalkyl, carboxyl, alkoxyalkyl, alkoxycarbonyl. Compounds of specific interest are (2,3,4-trihydroxy)-benzylhydrazine, 1-(D,L-seryl-2 (2,3,4-trihydroxybenzyl)hydrazine (Benserazide) and 1-(3-hydroxylbenzyl)-1-methylhydrazine.

Another more highly preferred class of compounds consists of those compounds wherein each of R³⁶ and R³⁷ is independently selected from hydrido, alkyl and amino and n is two; wherein each of R³⁸ through R⁴² is independently selected from hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl and carboxyalkyl. Compounds of specific interest are 2-hydrazino-2-methyl-3-(3,4-dihydroxyphenyl)propionic acid (Carbidopa), α -(monofluoromethyl)dopa and α -(difluoromethyl)dopa.

Another class of compounds from which a suitable dopa-decarboxylase inhibitor compound may be selected to provide the conjugate first residue is represented by Formula VII

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wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy and formyl; wherein each of R⁴⁹ and R⁵⁰ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl and

25

$\begin{array}{c} \text{O} \\ \parallel \\ \text{-CR}^{\text{51}} \end{array}$ wherein R⁵¹ is selected from hydroxy, alkoxy, aryloxy, aralkoxy, amino, monoalkylamino and dialkylamino with the proviso that R⁴⁹ and R⁵⁰ cannot both be carboxyl at the same time, and with the further proviso that at least one of R⁴⁵ through R⁴⁸ is a primary or secondary amino group or a carboxyl group; or a pharmaceutically-acceptable salt thereof.

A preferred class of compounds within Formula VII consists of those compounds wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, 5 aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴⁹ and R⁵⁰ is independently selected from 10 hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyalkyl and alkanoyl and

$\begin{array}{c} \text{O} \\ \parallel \\ -\text{CR}^{51}-$ wherein R⁵¹ is selected from hydroxy, alkoxy, 15 phenoxy, benzyloxy, amino, monoalkylamino and dialkylamino.

A more preferred class of compounds within Formula VII consists of those compounds wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, 20 hydroxy, alkyl, benzyl, phenyl, alkoxy, benzyloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴⁹ and R⁵⁰ is independently 25 selected from hydrido, alkyl, benzyl, phenyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyalkyl and alkanoyl and

$\begin{array}{c} \text{O} \\ \parallel \\ -\text{CR}^{51}-$ wherein R⁵¹ is selected from hydroxy, alkoxy, amino 30 and monoalkylamino.

An even more preferred class of compounds of Formula VII consists of those compounds wherein each of R⁴⁵

through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴⁹ and R⁵⁰ is
5 independently selected from hydrido, alkyl, amino, monoalkylamino, carboxyalkyl and

O
||
-CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy, amino and monoalkylamino.

10

A highly preferred class of compounds within Formula VII consists of those compounds wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, alkoxy and hydroxyalkyl; wherein each of R⁴⁹ and R⁵⁰ is independently selected from alkyl, amino, monoalkylamino, and

20

O
||
-CR⁵¹ wherein R⁵¹ is selected from hydroxy, methoxy, ethoxy, propoxy, butoxy, amino, methylamino and ethylamino.
A more highly preferred class of compounds within Formula VII consists of those compounds wherein said inhibitor compound is selected from endo-2-amino-1,2,3,4-tetrahydro-1,2-ethanonaphthalene-2-carboxylic acid; ethyl-
25 endo-2-amino-1,2,3,4-tetrahydro-1,4-ethano-naphthalene-2-carboxylate hydrochloride; exo-2-amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylic acid; and ethyl-exo-2-amino-1,2,3,4-tetrahydro-1,4-ethano-naphthalene-2-carboxylate hydrochloride.

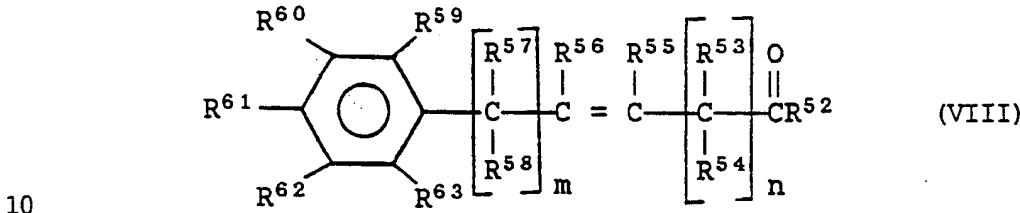
30

Another family of specific dopa-decarboxylase inhibitor compounds consists of 2,3-dibromo-4,4-bis(4-ethylphenyl)-2-butenoic acid;

- 3-bromo-4-(4-methoxyphenyl)-4-oxo-2-butenoic acid;
N-(5'-phosphopyridoxyl)-L-3,4-dihydroxyphenylalanine;
N-(5'-phosphopyridoxyl)-L-m-aminotyrosine;
D,L- β -(3,4-dihydroxyphenyl)lactate;
5 D,L- β -(5-hydroxyindolyl-3)lactate;
2,4-dihydroxy-5-(1-oxo-2-propenyl)benzoic acid;
2,4-dimethoxy-5-[1-oxo-3-(2,3,4-trimethoxyphenyl-2-propenyl]benzoic acid;
2,4-dihydroxy-5-[1-oxo-3-(2-thienyl)-2-propenyl] benzoic
10 acid;
2,4-dihydroxy-5-[3-(4-hydroxyphenyl)-1-oxo-2-propenyl] benzoic acid;
5-[3-(4-chlorophenyl)-1-oxo-2-propenyl]-2,4-dihydroxy
benzoic acid;
15 2,4-dihydroxy-5-(1-oxo-3-phenyl-2-propenyl)benzoic acid;
2,4-dimethoxy-5-[1-oxo-3-(4-pyridinyl)-2-propenyl] benzoic
acid;
5-[3-(3,4-dimethoxyphenyl)-1-oxo-2-propenyl]-2,4 dimethoxy
benzoic acid;
20 2,4-dimethoxy-5-(1-oxo-3-phenyl-2-propenyl)benzoic acid;
5-[3-(2-furanyl)-1-oxo-2-propenyl]-2,4-dimethoxy benzoic
acid;
2,4-dimethoxy-5-[1-oxo-3-(2-thienyl)-2-propenyl] benzoic
acid;
25 2,4-dimethoxy-5-[3-(4-methoxyphenyl)-1-oxo-2-propenyl]
benzoic acid;
5-[3-(4-chlorophenyl)-1-oxo-2-propenyl]-2,4-dimethoxy
benzoic acid; and
5-[3-[4-(dimethylamino)phenyl]-1-oxo-2-propenyl]-2,4
30 dimethoxy benzoic acid.

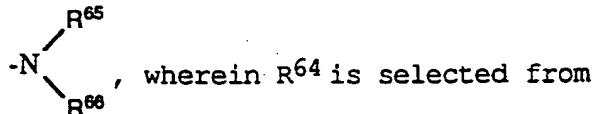
Another class of compounds from which a suitable dopa-decarboxylase inhibitor may be selected to provide the conjugate first residue is represented by Formula VIII:

5



10

wherein R⁵² is selected from hydrido, OR⁶⁴ and



- wherein R⁶⁴ is selected from
 15 hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl and phenyl, and wherein each of R⁶⁵ and R⁶⁶ is independently selected from hydrido, alkyl, alkanoyl, amino, monoalkylamino, dialkylamino, phenyl and phenalkyl; wherein each of R⁵³, R⁵⁴ and R⁵⁷ through R⁶³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxycarbonyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein each of R⁵⁵ and R⁵⁶ is
 20 independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl, halo, hydroxyalkyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein each of R⁵⁵ and R⁵⁶ is
 25 independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl, halo, haloalkyl, hydroxyalkyl and carboxyalkyl; wherein each of m and n is a number independently selected from zero through six, inclusive; or a pharmaceutically-acceptable salt
 30 thereof.

A preferred class of compounds of Formula VIII consists of those compounds wherein R⁵² is OR⁶⁴ wherein R⁶⁴

is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, benzyl and phenyl; wherein each of R⁵³, R⁵⁴ and R⁵⁷ through R⁶³ is independently selected from hydrido, alkyl, cycloalkyl, hydroxy, alkoxy, benzyl and phenyl; wherein each of R⁵⁵ and R⁵⁶ is independently selected from hydrido, alkyl, cycloalkyl, benzyl and phenyl; wherein each of m and n is a number independently selected from zero through three, inclusive.

10 A more preferred class of compounds of Formula VIII consists of those compounds wherein R⁵² is OR⁶⁴ wherein R⁶⁴ is selected from hydrido and lower alkyl; wherein each of R⁵³ through R⁵⁸ is hydrido; wherein each of R⁵⁹ through R⁶³ is independently selected from hydrido, alkyl, hydroxy and alkoxy, with the proviso that two of the R⁵⁹ through R⁶³ substituents are hydroxy; wherein each of m and n is a number independently selected from zero through two, inclusive.

20 A preferred compound within Formula IX is 3-(3,4-dihydroxyphenyl)-2-propenoic acid, also known as caffeic acid.

25 Another class of compounds from which a suitable dopa-decarboxylase inhibitor compound may be selected to provide the conjugate first residue is a class of aromatic amino acid compounds comprising the following subclasses of compounds:

- 30 - amino-haloalkyl-hydroxyphenyl propionic acids, such as 2-amino-2-fluoromethyl-3hydroxy-phenylpropionic acid;
- 35 - alpha-halomethyl-phenylalanine derivatives such as alpha-fluoroethylphenethylamine; and

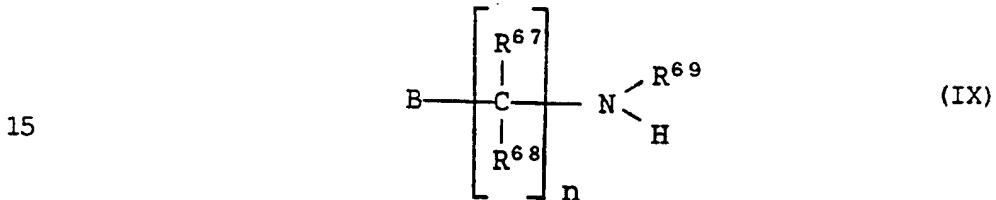
- indole-substituted halomethylamino acids.

Still other classes of compounds from which a
5 suitable dopa-decarboxylase inhibitor compound may be
selected to provide the conjugate first residue are as
follows:

- isoflavone extracts from fungi and
10 streptomyces, such as 3',5,7-trihydroxy-4',6-
dimethoxyisoflavone, 3',5,7-trihydroxy-4',8-
dimethoxyisoflavone and 3',8-dihydroxy-4',6,7-
trimethoxyisoflavone;
- sulfinyl substituted dopa and tyrosine
15 derivatives such as shown in U.S. Patent No.
4,400,395 the content of which is incorporated
herein by reference;
- hydroxycoumarin derivatives such as shown in
20 U.S. Patent No. 3,567,832, the content of
which is incorporated herein by reference;
- 1-benzylcyclobut enyl alkyl carbamate
25 derivatives such as shown in U.S. Patent No.
3,359,300, the content of which is
incorporated herein by reference;
- arylthienyl-hydroxylamine derivatives such as
30 shown in U.S. Patent No. 3,192,110, the
content of which is incorporated herein by
reference; and
- β -2-substituted-cyclohepta-pyrrol-8-1H-on-7-yl
35 alanine derivatives.

Suitable dopamine- β -hydroxylase inhibitors may be generally classified mechanistically as chelating-type inhibitors, time-dependent inhibitors and competitive
5 inhibitors.

A class of compounds from which a suitable dopamine- β -hydroxylase inhibitor may be selected to provide the conjugate first residue consists of time-dependent
10 inhibitors represented by Formula IX:



wherein B is selected from aryl, an ethylenic moiety, an
20 acetylenic moiety and an ethylenic or acetylenic moiety substituted with one or more radicals selected from substituted or unsubstituted alkyl, aryl and heteroaryl; wherein each of R⁶⁷ and R⁶⁸ is independently selected from hydrido, alkyl, alkenyl and alkynyl; wherein R⁶⁹ is
25 selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is a number
30 selected from zero through five.

A preferred class of compounds of Formula IX consists of those compounds wherein B is phenyl or hydroxyphenyl; wherein R⁶⁷ is ethenyl or ethynyl; or an

acetylenic moiety substituted with an aryl or heteroaryl radical; and wherein n is a number from zero through three.

Another preferred class of compounds of Formula IX consists of those compounds wherein B is an ethylenic or acetylenic moiety incorporating carbon atoms in the beta- and gamma-positions relative to the nitrogen atom; and wherein n is zero or one. More preferred are compounds wherein the ethylenic or acetylenic moiety is substituted at the gamma carbon with an aryl or heteroaryl radical. Even more preferred are compounds wherein said aryl radical is selected from phenyl, 2-thiophene, 3-thiophene, 2-furanyl, 3-furanyl, oxazolyl, thiazolyl and isoxazolyl, any one of which radicals may be substituted with one or more groups selected from halo, hydroxyl, alkyl, haloalkyl, cyano, alkoxy, alkoxyalkyl and cycloalkyl. More highly preferred are compounds wherein said aryl radical is selected from phenyl, hydroxyphenyl, 2-thiophene and 2-furanyl; and wherein each of R⁶⁷, R⁶⁸ and R⁶⁹ is hydrido.

20

A family of specifically-preferred compounds within Formula IX consists of the compounds 3-amino-2-(2'-thienyl)propene; 3-amino-2-(2'-thienyl)butene; 3-(N-methylamino)-2-(2'-thienyl)propene; 3-amino-2-(3'-thienyl)propene; 3-amino-2-(2'furanyl)propene; 3-amino-2-(3'-furanyl)propene; 1-phenyl-3aminopropyne; and 3-amino-2-phenylpropene. Another family of specifically-preferred compounds of Formula VIII consists of the compounds (\pm)4-amino-3-phenyl-1butyne; (\pm)4-amino-3-(3'-hydroxyphenyl)-1-butyne; (\pm)4-amino-3-(4'-hydroxyphenyl)-1-butyne; (\pm)4-amino-3-phenyl-1-butene; (\pm)4-amino-3-(3'-hydroxyphenyl)-1-butene; and (\pm)4-amino-3-(4'-hydroxyphenyl)-1-butene.

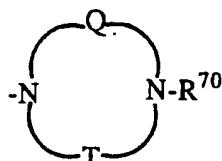
Another class of compounds from which a suitable dopamine- β -hydroxylase inhibitor may be selected to provide the conjugate first residue is represented by Formula X:

5



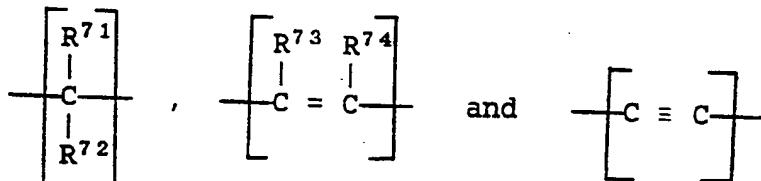
(X)

wherein W is selected from alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl; wherein Y is
10 selected from



wherein R⁷⁰ is selected from hydrido, alkyl, cycloalkyl,
15 hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxy carbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each
20 of Q and T is one or more groups independently selected from

25



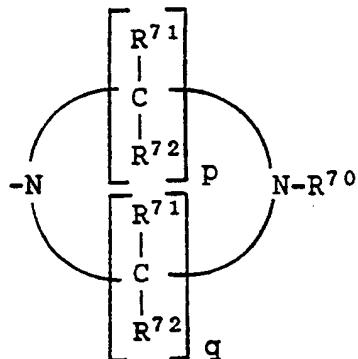
wherein each of R⁷¹ through R⁷⁴ is independently selected
from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl,
30 aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino,

monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; or a pharmaceutically-acceptable salt thereof.

- 5 A preferred class of compounds within Formula X consists of compounds wherein W is heteroaryl and Y is

10

15



- wherein R⁷⁰ is selected from hydrido, alkyl, amino, monoalkylamino, dialkylamino, phenyl and phenalkyl; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, hydroxy, alkyl, phenoxyl, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive.

25

- A more preferred class of compounds of Formula X consists of wherein R⁷⁰ is selected from hydrido, alkyl, amino and monoalkylamino; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive. Even more preferred are compounds wherein R⁷⁰ is selected from hydrido, alkyl and amino; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, amino,

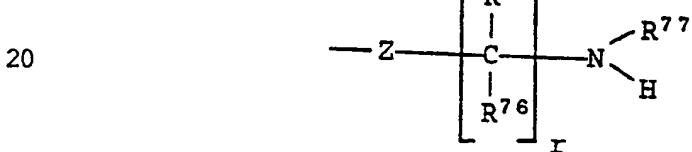
monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three. Most preferred are compounds wherein R⁷⁰ is hydrido; wherein each of R⁷¹ and R⁷² is hydrido; and wherein each of p and q is two.

Another class of compounds from which a suitable dopamine- β -hydroxylase inhibitor may be selected to provide the conjugate first residue is represented by Formula XI:

10



wherein E is selected from alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, 15 aralkyl, heterocycloalkyl and heteroaryl; wherein F is selected from



25 wherein Z is selected from O, S and N-R⁷⁸; wherein each of R⁷⁵ and R⁷⁶ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, minoalkylamino, 30 dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R⁷⁵ and R⁷⁶ may form oxo or thio; wherein r is a number selected from zero through six, inclusive; wherein each of R⁷⁷ and R⁷⁸ is independently selected from hydrido, alkyl, cycloalkyl,

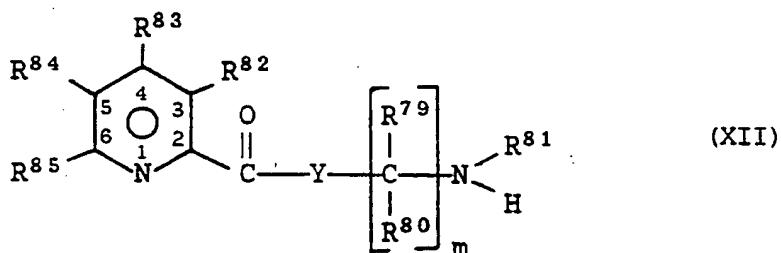
hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; or a

- 5 pharmaceutically acceptable salt thereof.

Another class of compounds from which a suitable dopamine- β -hydroxylase inhibitor may be selected to provide the conjugate first residue is represented by Formula XII:

10

15



wherein each of R⁸² through R⁸⁵ is independently selected from hydrido, alkyl, haloalkyl, mercapto, alkylthio, cyano, alkoxy, alkoxyalkyl and cycloalkyl; wherein Y is selected 20 from oxygen atom and sulfur atom; wherein each of R⁷⁹ and R⁸⁰ is independently selected from hydrido and alkyl; wherein R⁸¹ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, 25 cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein m is a number from one through six; or a pharmaceutically-acceptable salt thereof.

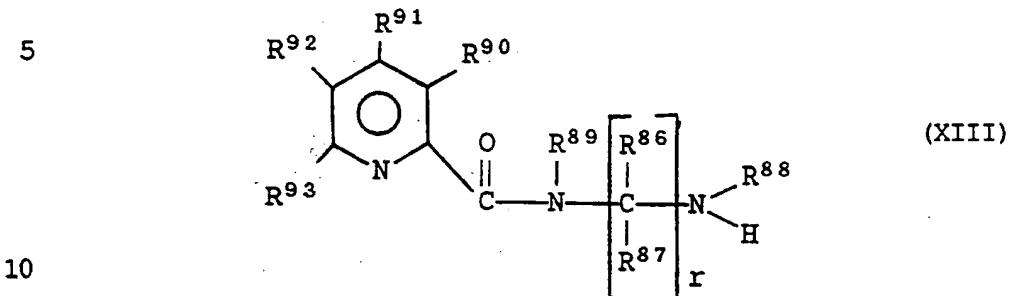
30

A preferred family of compounds of Formula XII consists of those compounds wherein each of R⁸² through R⁸⁵ is independently selected from hydrido, alkyl and haloalkyl; wherein Y is selected from oxygen atom or sulfur atom; wherein each of R⁷⁹, R⁸⁰ and R⁸¹ is independently

hydrido and alkyl; and wherein m is a number selected from one through four, inclusive.

- A family of preferred specific compounds within
- 5 Formula XII consists of the following compounds:
aminomethyl-5-n-butylthiopicolinate;
aminomethyl-5-n-butylpicolinate;
2'-aminoethyl-5-n-butylthiopicolinate;
2'-aminoethyl-5-n-butylpicolinate;
- 10 (2'-amino-1',1'-dimethyl)ethyl-5-n-butylthiopicolinate;
(2'-amino-1',1'-dimethyl)ethyl-5-n-butylpicolinate;
(2'-amino-1'-methyl)ethyl-5-n-butylthiopicolinate;
(2'-amino-1'-methyl)ethyl-5-n-butylpicolinate;
3'-aminopropyl-5-n-butylthiopicolinate;
- 15 3'-aminopropyl-5-n-butylpicolinate;
(2'-amino-2'-methyl)propyl-5-n-butylthiopicolinate;
(2'-amino-2'-methyl)propyl-5-n-butylpicolinate;
(3'-amino-1',1'-dimethyl)propyl-5-n-butylthiopicolinate;
(3'-amino-1',1'-dimethyl)propyl-5-n-butylpicolinate;
- 20 (3'-amino-2',2'-dimethyl)propyl-5-n-butylthiopicolinate;
(3'-amino-2',2'-dimethyl)propyl-5-n-butylpicolinate;
2'-aminopropyl-5-n-butylthiopicolinate;
2'-aminopropyl-5-n-butylpicolinate;
4'-aminobutyl-5-n-butylthiopicolinate;
- 25 4'-amino-3'-methyl)butyl-5-n-butylthiopicolinate;
(3'-amino-3'-methyl)butyl-5-n-butylpicolinate;
and (3'-amino-3'-methyl)butyl-5-n-butylpicolinate.

Another preferred class of compounds within Formula XII consists of those compounds of Formula XIII:



- wherein each of R⁸⁶, R⁸⁷ and R⁹⁰ through R⁹³ is independently selected from hydrido, hydroxy, alkyl,
 15 cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R⁸⁶ and R⁸⁷ together may form oxo or thio;
 20 wherein r is a number selected from zero through six, inclusive; wherein each of R⁸⁸ and R⁸⁹ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino,
 25 monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl.

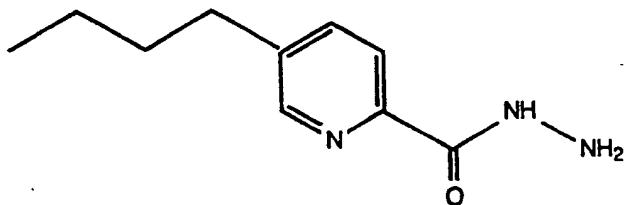
- A more preferred class of compounds within Formula XIII consists of those compounds wherein each of R⁸⁶, R⁸⁷ and R⁹⁰ through R⁹³ is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; wherein r is a number selected from zero through 35 four, inclusive; wherein each of R⁸⁸ and R⁸⁹ is

independently selected from hydrido, alkyl, amino, monoalkylamino, dialkylamino, phenyl and phenalkyl.

An even more preferred class of compounds within
5 Formula XIII consists of those compounds wherein each of R⁸⁶, R⁸⁷ and R⁹⁰ through R⁹³ is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein r is a number selected from zero through three, inclusive; and
10 wherein each of R⁸⁸ and R⁸⁹ is selected from hydrido, alkyl, amino and monoalkylamino. Most preferred are compounds wherein each of R⁹⁰ through R⁹³ is independently selected from hydrido and alkyl; wherein each of R⁸⁶ and R⁸⁷ is hydrido; wherein r is selected from zero, one and
15 two; wherein R⁸⁸ is selected from hydrido, alkyl and amino; and wherein R⁸⁹ is selected from hydrido and alkyl. Especially preferred within this class is the compound 5-n-butylpicolinic acid hydrazide (fusaric acid hydrazide) shown below:

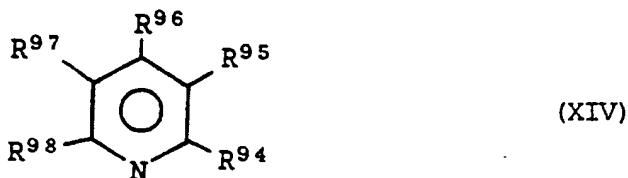
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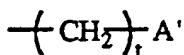
Another class of compounds from which a suitable dopamine- β -hydroxylase inhibitor compound may be selected to provide the conjugate first residue is represented by Formula XIV:

5



10

wherein each of R⁹⁴ through R⁹⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, aryloxy, alkoxy, alkylthio, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, amido, alkylamido, hydroxyamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, tetrazolyl, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, formoyl and alkoxy carbonyl; with the proviso that at least one of R⁹⁴ through R⁹⁸ is

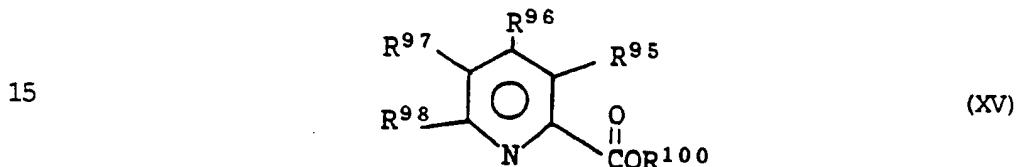


25 wherein A' is $-\text{CR}^{99}$ or $-\text{N}^{\text{R}^{101}}_{\text{R}^{102}}$ wherein R⁹⁹ is selected from hydrido, alkyl, hydroxy, alkoxy, alkylthio, phenyl, phenoxy, benzyl, benzyloxy,

30 $-\text{OR}^{100}$ and $-\text{N}^{\text{R}^{103}}_{\text{R}^{104}}$, wherein R¹⁰⁰ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenyl and benzyl; each of R¹⁰¹, R¹⁰², R¹⁰³ and R¹⁰⁴ is independently

selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl,
 5 arylsulfinyl and arylsulfonyl; wherein t is a number selected from zero through four, inclusive; or a pharmaceutically-acceptable salt thereof.

A preferred family of compounds within Formula
 10 XIV consists of those compounds characterized as chelating-type inhibitors of Formula XV:

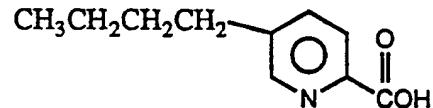


20 wherein each of R95 through R98 is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, phenyl, benzyl, alkoxy, phenoxy, benzyloxy, alkoxyalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, amido, alkylamido, hydroxyamino, carboxyl, carboxyalkyl, alkanoyl,
 25 cyanoamino, carboxyl, thiocarbamoyl, aminomethyl, nitro, formoyl, formyl and alkoxycarbonyl; and wherein R100 is selected from hydrido, alkyl, phenyl and benzyl.

A class of specifically-preferred compounds of
 30 Formula XV consists of
 5-n-butylicolic acid (fusaric acid);
 5-ethylpicolinic acid;
 picolinic acid;
 5-nitropicolinic acid;
 35 5-aminopicolinic acid;

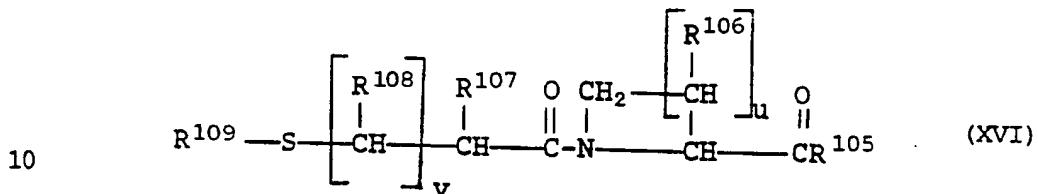
- 5-N-acetylaminopicolinic acid;
5-N-propionylaminopicolinic acid;
5-N-hydroxyaminopicolinic acid;
5-iodopicolinic acid;
5 5-bromopicolinic acid;
5-chloropicolinic acid;
5-hydroxypicolinic acid
5-methoxypicolinic acid;
5-N-propoxypicolinic acid;
10 5-N-butoxypicolinic acid;
5-cyanopicolinic acid;
5-carboxylic acid;
5-n-butyl-4-nitropicolinic acid;
5-n-butyl-4-methoxypicolinic acid;
15 5-n-butyl-4-ethoxypicolinic acid;
5-n-butyl-4-aminopicolinic acid;
5-n-butyl-4-hydroxyaminopicolinic acid; and
5-n-butyl-4-methylpicolinic acid.

20 Especially preferred of the foregoing class of compounds of Formula XV is the compound 5-n-butylic acid (fusaric acid) shown below:



Another class of compounds from which a suitable dopamine- β -hydroxylase inhibitor may be selected to provide the conjugate first residue consists of azetidine-2-carboxylic acid derivatives represented by Formula XVI:

5



wherein R¹⁰⁵ is hydrido, hydroxy, alkyl, amino and alkoxy; wherein R¹⁰⁶ is selected from hydrido, hydroxy and alkyl; wherein each of R¹⁰⁷ and R¹⁰⁸ is independently selected from hydrido, alkyl and phenalkyl; wherein R¹⁰⁹ is selected from hydrido and



R¹¹⁰C- with R¹¹⁰ selected from alkyl, phenyl and phenalkyl; wherein u is a number from one to three, inclusive; and wherein v is a number from zero to two, inclusive; or a pharmaceutically-acceptable salt thereof.

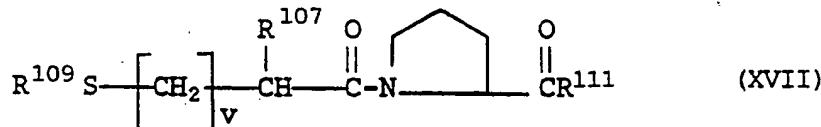
A preferred class of compounds within Formula XVI consists of those compounds wherein R¹⁰⁵ is selected from hydroxy and lower alkoxy; wherein R¹⁰⁶ is hydrido; wherein R¹⁰⁷ is selected from hydrido and lower alkyl; wherein R¹⁰⁸ is hydrido; wherein R¹⁰⁹ is selected from hydrido and



R¹¹⁰C- with R¹¹⁰ selected from lower alkyl and phenyl; wherein u is two; and wherein v is a number from zero to two, inclusive.

A more preferred class of compounds within Formula XVI consists of those compounds of Formula XVII:

5



- 10 wherein R¹¹¹ is selected from hydroxy and lower alkyl;
 wherein R¹⁰⁷ is selected from hydrido and lower alkyl;
 wherein R¹⁰⁹ is selected from hydrido and
 $\begin{array}{c} \text{O} \\ \parallel \\ \text{R}^{110}\text{C}- \end{array}$
 with R¹¹⁰ selected from lower alkyl and phenyl and v
 is a number from zero to two, inclusive.

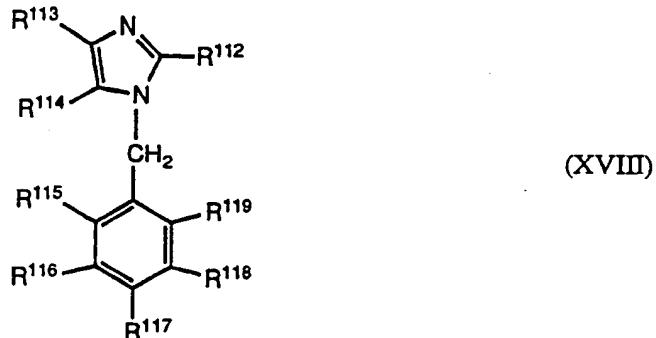
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- A more preferred class of compounds within Formula XVII consists of those compounds wherein R¹¹¹ is hydroxy; wherein R¹⁰⁷ is hydrido or methyl; wherein R¹⁰⁹ is hydrido or acetyl; and wherein n is a number from zero to
 20 two, inclusive.

- Most preferred within the class of compounds of Formula XVII are the compounds 1-(3-mercaptopro-2-methyl-1-oxopropyl)-L-proline and 1-(2-mercaptoproacetyl)-L-proline
 25 (also known as captopril).

Another class of compounds from which a suitable dopamine- β -hydroxylase inhibitor compound may be selected to provide the conjugate first residue is represented by Formula XVIII:

5



wherein each of R¹¹² through R¹¹⁹ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, 10 alkoxy, alkoxyalkyl, aralkyl, aryl, alkoxy carbonyl, hydroxyalkyl, halo, haloalkyl, cyano, amino, aminoalkyl, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, mercapto and alkylthio; or a pharmaceutically-acceptable salt thereof.

15

A first preferred class of compounds within Formula XVIII consists of those compounds wherein R¹¹² is selected from mercapto and alkylthio; wherein each of R¹¹³ and R¹¹⁴ is independently selected from hydrido, amino, 20 aminoalkyl, monoalkylamino, monoalkylaminoalkyl, carboxyl and carboxyalkyl; wherein each of R¹¹⁵ and R¹¹⁹ is hydrido; and wherein each of R¹¹⁶, R¹¹⁷ and R¹¹⁸ is independently selected from hydrido, hydroxy, alkyl, halo and haloalkyl; or a pharmaceutically-acceptable salt thereof.

25

A second preferred class of compounds within Formula XVIII consists of those compounds wherein R¹¹² is selected from amino, aminoalkyl, monoalkylamino, monoalkylaminoalkyl, carboxy and carboxyalkyl; wherein each 5 of R¹¹³, R¹¹⁴, R¹¹⁵ and R¹¹⁹ is hydrido; and wherein each of R¹¹⁶, R¹¹⁷ and R¹¹⁸ is independently selected from hydrido, hydroxy, alkyl, halo and haloalkyl; or a pharmaceutically-acceptable salt thereof.

10 Compounds which fall within any of the aforementioned inhibitor compounds, but which lack a reactive acid or amino moiety to form a cleavable bond, may be modified or derivatized to contain such acid or amino moiety. Examples of classes of such compounds lacking an 15 amino on acidic moiety are the following: 1-(3,5-dihaloaryl)imidazol-2-thione derivatives such as 1-(3,5-difluorobenzyl)imidazol-2thione; and hydroxyphenolic derivatives such as resorcinol.

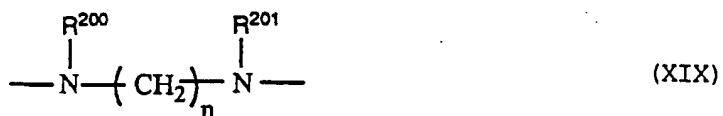
20 The first component used to form the conjugate of the invention provides a first residue derived from an inhibitor compound capable of inhibiting formation of a benzylhydroxylamine intermediate involved in the biosynthesis of an adrenergic neurotransmitter. This inhibitor compound 25 must contain a moiety convertible to a primary or secondary amino terminal moiety. An example of a moiety convertible to an amino terminal moiety is a carboxylic acid group reacted with hydrazine so as to convert the acid moiety to carboxylic acid hydrazide. The hydrazide moiety thus contains the 30 terminal amino moiety which may then be further reacted with

the carboxylic acid containing residue of the second component to form a hydrolyzable amide bond. Such hydrazide moiety thus constitutes a "linker" group between the first and second components of a conjugate of the invention.

5

Suitable linker groups may be provided by a class of diamino-terminated linker groups based on hydrazine as defined by Formula XIX:

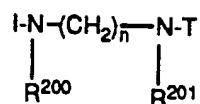
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15

wherein each of R²⁰⁰ and R²⁰¹ may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfino, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive. In Table I there is shown a class of specific examples of diamino-terminated linker groups within Formula XIX,

identified as Linker Nos. 1-73. These linker groups would be suitable to form a conjugate between a carbonyl moiety of an AII antagonist (designated as "I") and a carbonyl moiety of a carbonyl terminated second residue such as the carbonyl moiety
5 attached to the gamma carbon of a glutamyl residue (designated as "T").

TABLE I

5

I = inhibitor
 T = acetyl- γ -glutamyl

LINKER NO.	n	R ²⁰⁰	R ²⁰¹
1	0	H	H
2	0	CH ₃	H
3	0	C ₂ H ₅	H
4	0	C ₃ H ₇	H
5	0	CH(CH ₃) ₂	H
6	0	C ₄ H ₉	H
7	0	CH(CH ₃)CH ₂ CH ₃	H
8	0	C(CH ₃) ₃	H
9	0	C ₅ H ₉	H
10	0	C ₆ H ₁₁ (cyclo)	H
11	0	C ₆ H ₅	H
12	0	CH ₂ C ₆ H ₅	H
13	0	H	CH ₃

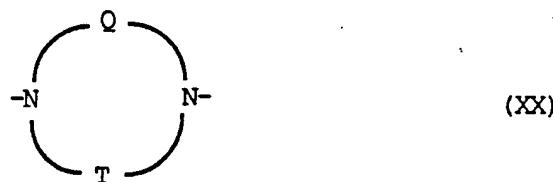
LINKER NO.	n	R ²⁰⁰	R ²⁰¹
14	0	H	C ₂ H ₅
5	15	0	H
	16	0	H
10	17	0	H
15	18	0	H
	19	0	H
20	20	0	H
	21	0	H
25	22	0	H
30	23	0	H
	24	0	H
35	25	0	C ₆ H ₁₃
	26	0	CH ₃
40	27	0	C ₂ H ₅
45	28	0	C ₃ H ₇
	29	0	CH(CH ₃) ₂
			CH(CH ₃) ₂

	LINKER NO.	n	R²⁰⁰	R²⁰¹
	30	0	C ₄ H ₉	C ₄ H ₉
5	31	0	CH(CH ₃)CH ₂ CH ₃	CH(CH ₃)CH ₂ CH ₃
	32	0	C(CH ₃) ₃	C(CH ₃) ₃
10	33	0	C ₅ H ₉	C ₅ H ₉
	34	0	C ₆ H ₁₃	C ₆ H ₁₃
15	35	0	C ₆ H ₁₁ (cyclo)	C ₆ H ₁₁ (cyclo)
20	36	0	C ₆ H ₅	C ₆ H ₅
	37	0	CH ₂ C ₆ H ₅	CH ₂ C ₆ H ₅
25	38	3	H	H
	39	3	CH ₃	H
30	40	3	H	CH ₃
	41	3	C ₆ H ₅	H
35	42	3	H	C ₆ H ₅
40	43	3	CH ₃	C ₆ H ₅
	44	3	C ₆ H ₅	CH ₃

LINKER NO.	n	R ²⁰⁰	R ²⁰¹
	45	3	CH ₂ C ₆ H ₅
5	46	3	H
	47	4	H
10	48	4	CH ₃
	49	4	H
15	50	4	C ₆ H ₅
20	51	4	H
	52	4	C ₆ H ₅
25	53	4	C ₆ H ₅
	54	4	CH ₂ C ₆ H ₅
30	55	4	H
	56	5	H
35	57	5	CH ₃
	58	5	H
	59	5	C ₆ H ₅
45	60	5	H
			C ₆ H ₅

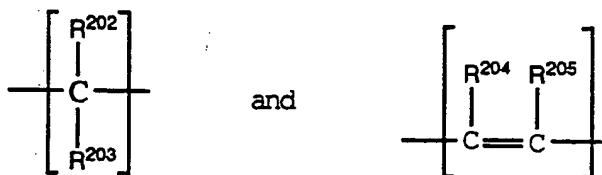
LINKER NO.	n	R ²⁰⁰	R ²⁰¹
	61	5	CH ₃
5	62	5	C ₆ H ₅
	63	5	CH ₂ C ₆ H ₅
10	64	5	H
	65	6	H
15	66	6	CH ₃
20	67	6	H
	68	6	C ₆ H ₅
25	69	6	H
	70	6	CH ₃
30	71	6	C ₆ H ₅
	72	6	CH ₂ C ₆ H ₅
35	73	6	H
			CH ₂ C ₆ H ₅

Another class of suitable diamino terminal linker groups is defined by Formula XX:



5

wherein each of Q and T is one or more groups independently selected from

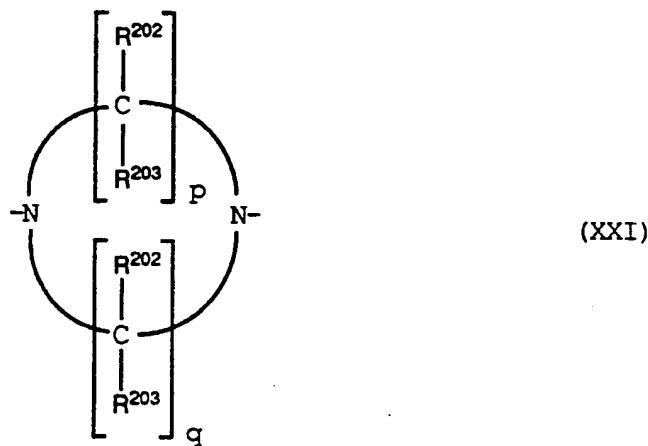


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wherein each of R²⁰² through R²⁰⁵ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

A preferred class of linker groups within Formula IV is defined by Formula XXI:

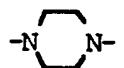
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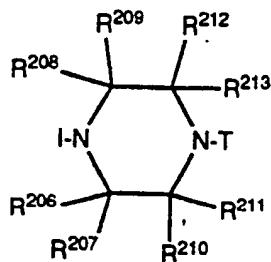
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wherein each of R²⁰² and R²⁰³ is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino,
5 monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; with the proviso that when each of R²⁰² and R²⁰³ is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then
10 the carbon to which R²⁰² or R²⁰³ is attached in Formula XXI is not adjacent to a nitrogen atom of Formula XXI.

A more preferred class of linker groups of Formula V consists of divalent radicals wherein each of R²⁰² and R²⁰³
15 is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive. Even more preferred are linker groups wherein each of R²⁰² and R²⁰³
20 is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three. Most preferred is a linker group wherein each of R²⁰² and R²⁰³ is hydrido; and wherein each of p and q is two; such most preferred linker
25 group is derived from a piperazinyl group and has the structure



In Table II there is shown a class of specific examples of cyclized, diamino-terminated linker groups within Formula XXI. These linker groups, identified as Linker Nos. 74-95, would be suitable to form a conjugate between a carbonyl moiety of an AII antagonist (designated as "I") and a carbonyl moiety of carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

TABLE II

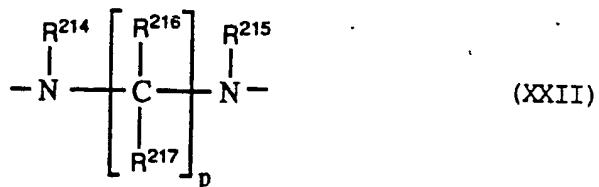
I = inhibitor
T = acetyl- γ -glutamyl

LINKER NO.	R ²⁰⁶	R ²⁰⁷	R ²⁰⁸	R ²⁰⁹	R ²¹⁰	R ²¹¹	R ²¹²	R ²¹³
74	H	H	H	H	H	H	H	H
75	CH ₃	H	H	H	H	H	H	H
76	H	H	H	H	CH ₃	H	H	H
77	CH ₃	H	H	H	CH ₃	H	H	H
78	CH ₃	H	CH ₃	H	H	H	H	H
79	CH ₃	H	H	H	H	H	CH ₃	H
80	CH ₃	CH ₃	H	H	H	H	H	H
81	H	H	H	H	CH ₃	CH ₃	H	H
82	CH ₃	CH ₃	H	H	CH ₃	CH ₃	H	H
83	CH ₃	CH ₃	CH ₃	CH ₃	H	H	H	H
84	CH ₃	CH ₃	H	H	H	H	CH ₃	CH ₃

45

LINKER NO.	R ²⁰⁶	R ²⁰⁷	R ²⁰⁸	R ²⁰⁹	R ²¹⁰	R ²¹¹	R ²¹²	R ²¹³
	85	H	H	H	H	CH ₃	CH ₃	CH ₃
5	86	C ₆ H ₅	H	H	H	H	H	H
	87	H	H	H	H	C ₆ H ₅	H	H
10	88	C ₆ H ₅	H	H	H	C ₆ H ₅	H	H
	89	C ₆ H ₅	H	H	H	H	H	C ₆ H ₅
15	90	C ₆ H ₅	H	C ₆ H ₅	H	H	H	H
20	91	CH ₂ C ₆ H ₅	H	H	H	H	H	H
	92	H	H	H	H	CH ₂ C ₆ H ₅	H	H
25	93	CH ₂ C ₆ H ₅	H	H	H	CH ₂ C ₆ H ₅	H	H
	94	CH ₂ C ₆ H ₅	H	H	H	H	H	CH ₂ C ₆ H ₅
30	95	CH ₂ C ₆ H ₅	H	CH ₂ C ₆ H ₅	H	H	H	H

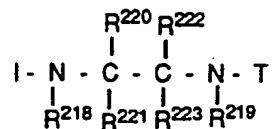
Another class of suitable diamino terminal linker groups is defined by Formula XXII:



5

wherein each of R²¹⁴ through R²¹⁷ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfino, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

A preferred class of linker groups within Formula VI consists of divalent radicals wherein each of R²¹⁴ and R²¹⁵ is hydrido; wherein each of R⁶² and R⁶³ is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three. A more preferred class of linker groups within Formula XXII consists of divalent radicals wherein each of R²¹⁴ and R²¹⁵ is hydrido; wherein each of R²¹⁶ and R²¹⁷ is independently selected from hydrido and alkyl; and wherein p is two. A specific example of a more preferred linker within Formula XXII is the divalent radical ethylenediamino. In Table III there is shown a class of specific examples of diamino-terminated linker groups within Formula XXII. These linker groups, identified as Linker Nos. 96-134, would be suitable to form a conjugate between a carbonyl moiety of an AII antagonist (designated as "I") and a carbonyl moiety of carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

TABLE III

5

I = inhibitor
 G = acetyl- γ -glutamyl

LINKER NO.	R ²¹⁸	R ²¹⁹	R ²²⁰	R ²²¹	R ²²²	R ²²³
96	H	H	H	H	H	H
97	H	H	H	H	H	CH ₃
98	H	H	H	CH ₃	H	H
99	H	H	H	CH ₃	H	CH ₃
100	CH ₃	H	H	H	H	H
101	H	CH ₃	H	H	H	H
102	H	H	H	H	CH ₃	CH ₃
103	H	H	CH ₃	CH ₃	H	H
104	CH ₃	CH ₃	H	H	H	H
105	H	H	H	H	H	C ₆ H ₅
106	H	H	H	C ₆ H ₅	H	H
107	H	H	H	C ₆ H ₅	H	C ₆ H ₅
108	C ₆ H ₅	H	H	H	H	H

LINKER NO.	R ²¹⁸	R ²¹⁹	R ²²⁰	R ²²¹	R ²²²	R ²²³
---------------	------------------	------------------	------------------	------------------	------------------	------------------

	109	H	C ₆ H ₅	H	H	H	H
5	110	H	H	H	H	C ₆ H ₅	C ₆ H ₅
10	111	H	H	C ₆ H ₅	C ₆ H ₅	H	H
	112	C ₆ H ₅	C ₆ H ₅	H	H	H	H
15	113	H	H	H	H	H	C ₂ H ₅
20	114	H	H	H	C ₂ H ₅	H	H
	115	H	H	H	C ₂ H ₅	H	C ₂ H ₅
25	116	C ₂ H ₅	H	H	H	H	H
	117	H	C ₂ H ₅	H	H	H	H
30	118	H	H	H	H	C ₂ H ₅	C ₂ H ₅
	119	H	H	C ₂ H ₅	C ₂ H ₅	H	H
35	120	C ₂ H ₅	C ₂ H ₅	H	H	H	H
40	121	CH ₃	H	C ₆ H ₅	H	H	H
	122	CH ₃	H	H	H	C ₆ H ₅	H
45	123	H	CH ₃	C ₆ H ₅	H	H	H

LINKER NO.	R ²¹⁸	R ²¹⁹	R ²²⁰	R ²²¹	R ²²²	R ²²³
	124	H	CH ₃	H	H	C ₆ H ₅
5	125	CH ₃	CH ₃	H	C ₆ H ₅	H
	126	CH ₃	CH ₃	H	H	H
10	127	H	H	H	H	CH ₂ C ₆ H ₅
	128	H	H	H	CH ₂ C ₆ H ₅	H
15	129	CH ₂ C ₆ H ₅	H	H	H	H
	130	H	CH ₂ C ₆ H ₅	H	H	H
20	131	CH ₃	H	CH ₂ C ₆ H ₅	H	H
	132	CH ₃	H	H	H	CH ₂ C ₆ H ₅
25	133	H	CH ₃	CH ₂ C ₆ H ₅	H	H
	134	H	CH ₃	H	H	CH ₂ C ₆ H ₅
30						

The term "hydrido" denotes a single hydrogen atom (H) which may be attached, for example, to an oxygen atom to form a hydroxyl group. Where the term "alkyl" is used, either alone or within other terms such as

- 5 "haloalkyl", "aralkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about ten carbon atoms unless otherwise specifically described. Preferred alkyl radicals are "lower alkyl" radicals having one to about five carbon atoms. The term "cycloalkyl"
- 10 embraces radicals having three to ten carbon atoms, such as cyclopropyl, cyclobutyl, cyclohexyl and cycloheptyl. The term "haloalkyl" embraces radicals wherein any one or more of the carbon atoms is substituted with one or more halo groups, preferably selected from bromo, chloro and fluoro.
- 15 Specifically embraced by the term "haloalkyl" are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for example, may have either a bromo, a chloro, or a fluoro atom within the group. Dihaloalkyl and polyhaloalkyl groups may be substituted with two or
- 20 more of the same halo groups, or may have a combination of different halo groups. Examples of a dihaloalkyl group are dibromomethyl, dichloromethyl and bromochloromethyl. Examples of a polyhaloalkyl are trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl and 2,2,3,3tetrafluoropropyl
- 25 groups. The term "alkoxy", embraces linear or branched oxy-containing radicals having an alkyl portion of one to about ten carbon atoms, such as methoxy, ethoxy, isopropoxy and butoxy. The term "alkylthio" embraces radicals containing a linear or branched alkyl group, of one to about ten carbon
- 30 atoms attached to a divalent sulfur atom, such as a methythio group. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl and biphenyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, phenylbutyl
- 35 and diphenylethyl. The terms "benzyl" and "phenylmethyl" are interchangeable. The terms "aryloxy" and "arylthio"

denote radical respectively, aryl groups having an oxygen or sulfur atom through which the radical is attached to a nucleus, examples of which are phenoxy and phenylthio. The terms "sulfinyl" and "sulfonyl", whether used alone or
5 linked to other terms, denotes respectively divalent radicals >SO and >SO_2 . The term "acyl" whether used alone, or within a term such as acyloxy, denotes a radical provided by the residue after removal of hydroxyl from an organic acid, examples of such radical being acetyl and
10 benzoyl. "Lower alkanoyl" is an example of a more preferred sub-class of acyl.

Within the classes of conjugates of the invention described herein are the pharmaceutically-
15 acceptable salts of such conjugates including acid addition salts and base addition salts. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical,
20 provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of conjugates of the invention may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic,
25 nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic,
30 gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, p-hydroxybenzoic, salicyclic, phenylacetic, mandelic, embonic (pamoic), methansulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, pantothenic,
35 benzenesulfonic, toluenesulfonic, sulfanilic, mesylic, cyclohexylaminosulfonic, stearic, algenic, β -hydroxy-

butyric, malonic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of the conjugates include metallic salts made from aluminium, calcium, lithium, magnesium, potassium, sodium and zinc or 5 organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding conjugates described herein by reacting, for 10 example, the appropriate acid or base with the conjugate.

Conjugates of the invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the 15 form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples 20 of appropriate acids are tartaric, diacetyl tartaric, dibenzoyl tartaric, ditoluoyl tartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for 25 separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting conjugates with an optically pure 30 acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically 35 active conjugates can likewise be obtained by utilizing optically active starting materials. These isomers may be

in the form of a free acid, a free base, an ester or a salt.

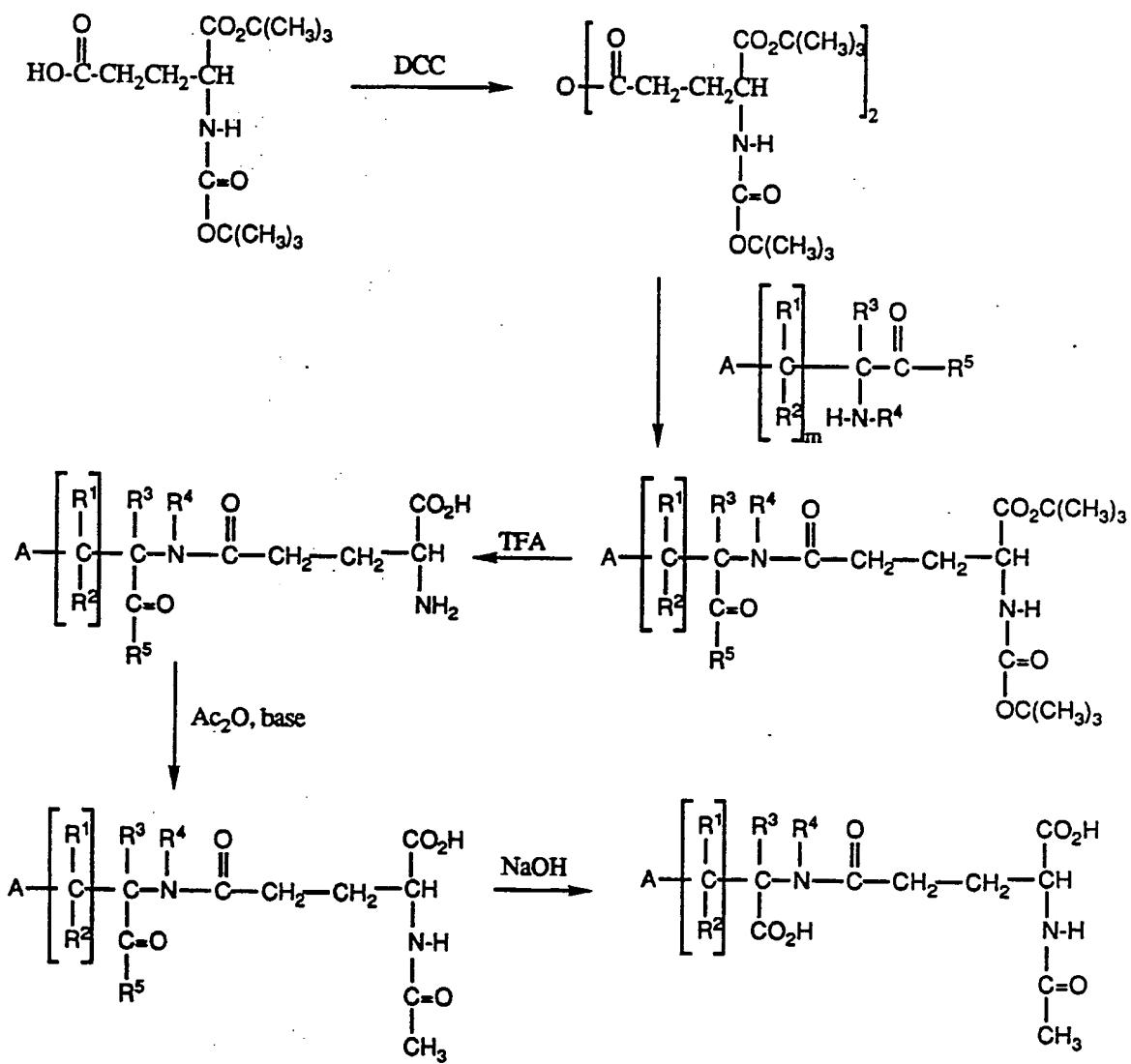
Synthetic Procedures

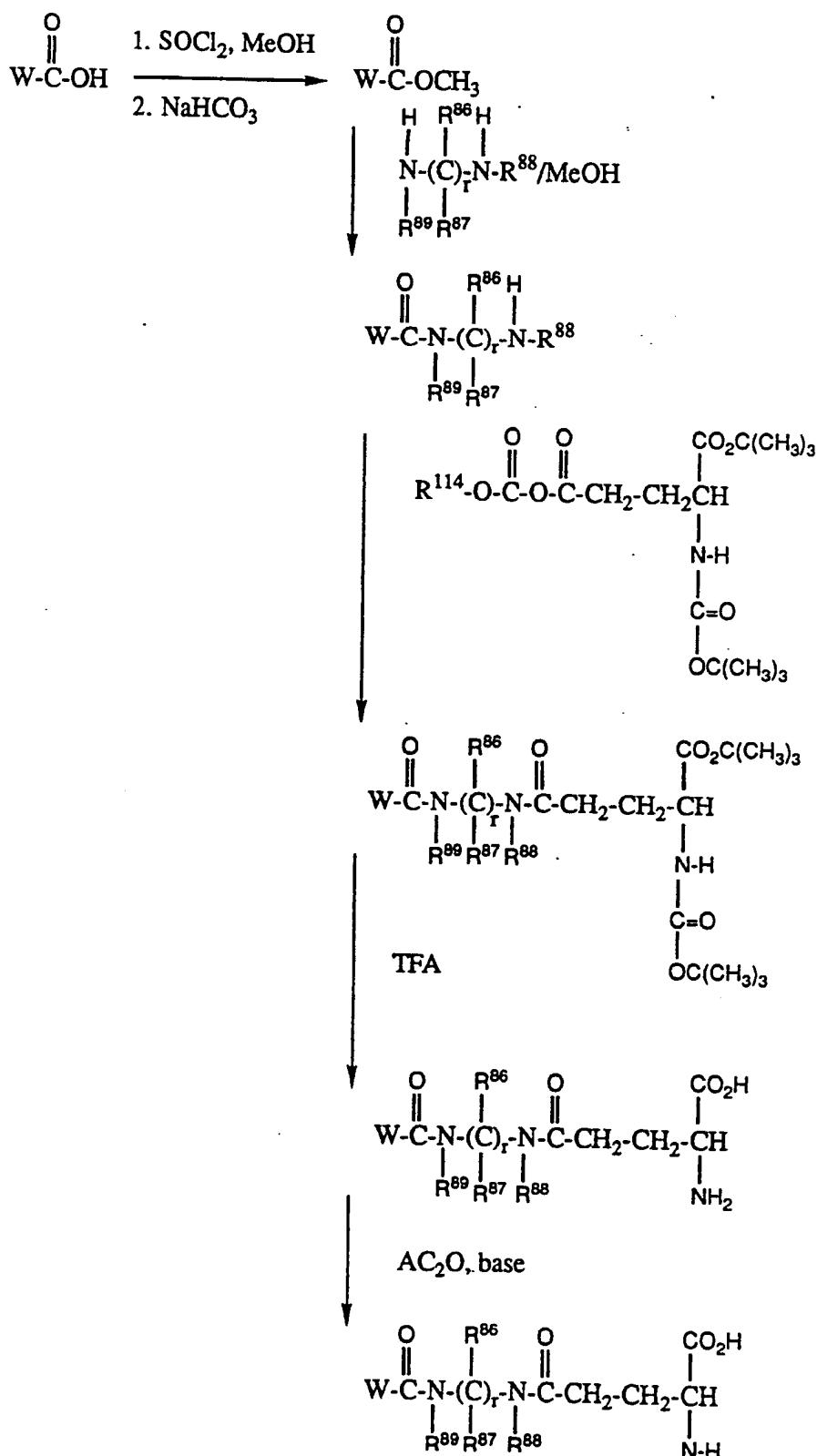
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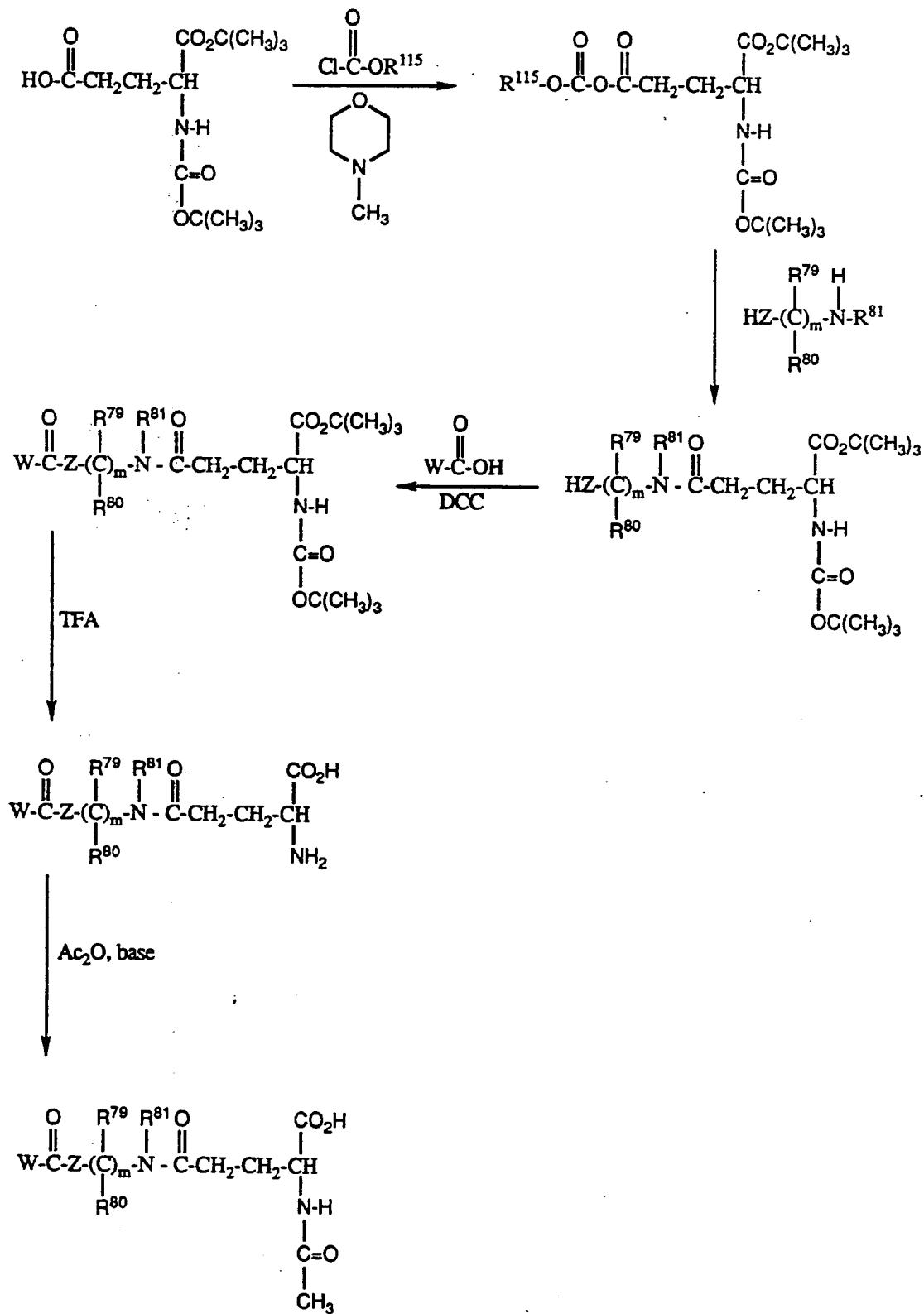
Conjugates of the invention are synthesized by reaction between precursors of the first and second residues. One of such precursors must contain a reactive acid moiety, and the other precursor must contain a reactive amino moiety, so that a conjugate is formed having a cleavable bond. Either precursor of the first and second residues may contain such reactive acid or amino moieties. Preferably, the precursors of the first residue are inhibitors of benzylhydroxyamine biosynthesis and will contain a reactive amino moiety or a moiety convertible to a reactive amino moiety. Many of the tyrosine hydroxylase inhibitors and dopa-decarboxylase inhibitors are characterized in having a reactive amino moiety. Inhibitor compounds lacking a reactive amino moiety, such as the dopamine- β -hydroxylase inhibitor fusaric acid, may be chemically modified to provide such reactive amino moiety. Chemical modification of these inhibitor compounds lacking a reactive amino group may be accomplished by reacting an acid or an ester group on the inhibitor compound with an amino compound, that is, a compound having at least one reactive amino moiety and another reactive hetero atom selected from O, S and N. A suitable amino compound would be a diamino compound such as hydrazine or urea. Hydrazine, for example, may be reacted with the acid or ester moiety of the inhibitor compound to form a hydrazone derivative of such inhibitor compound.

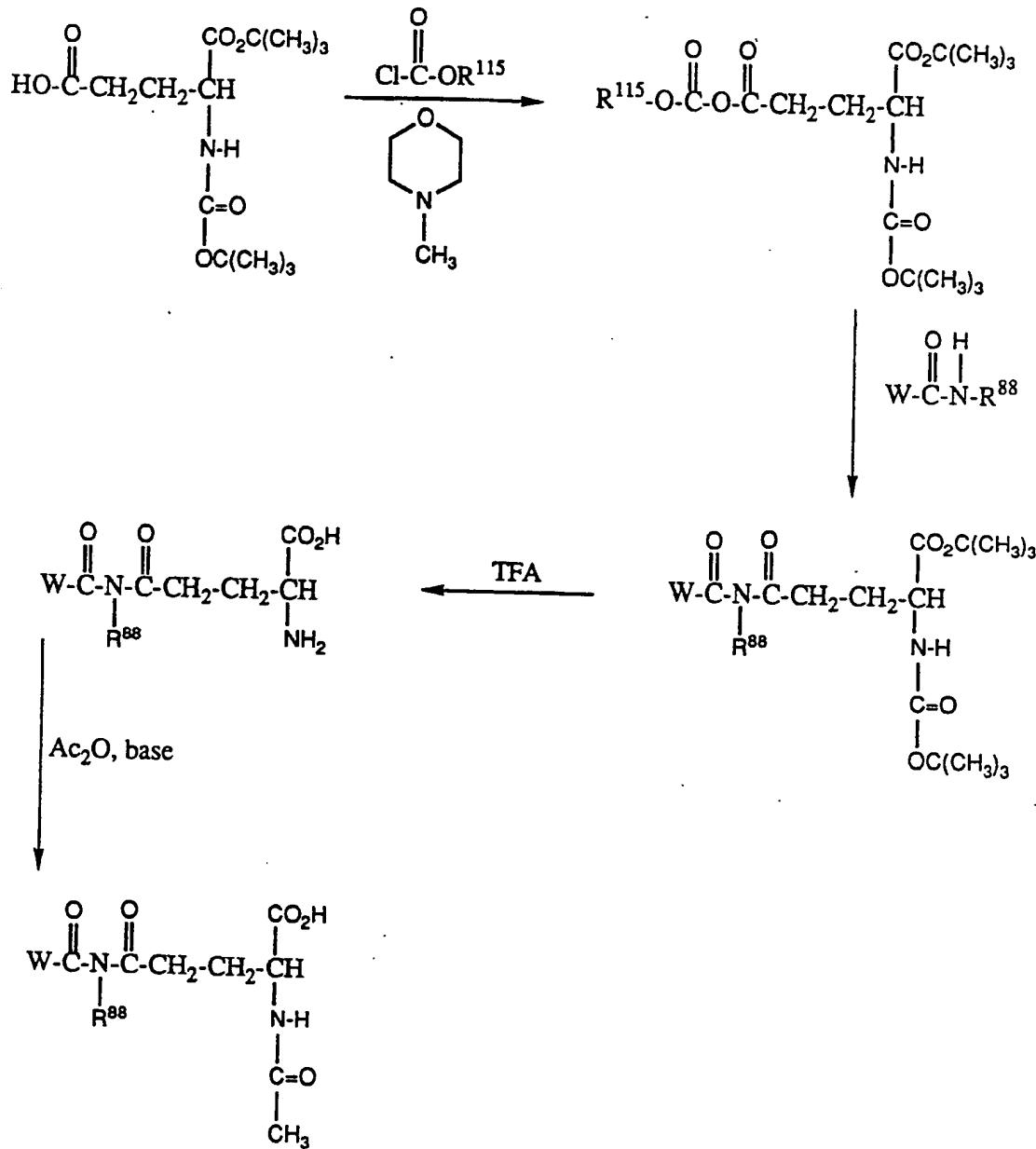
The dopamine- β -hydroxylase inhibitor compound 5-butyl-n-butylicolic acid (fusaric acid) may be used as a model compound to illustrate the chemical modification of an acid-containing inhibitor compound to make a reactive

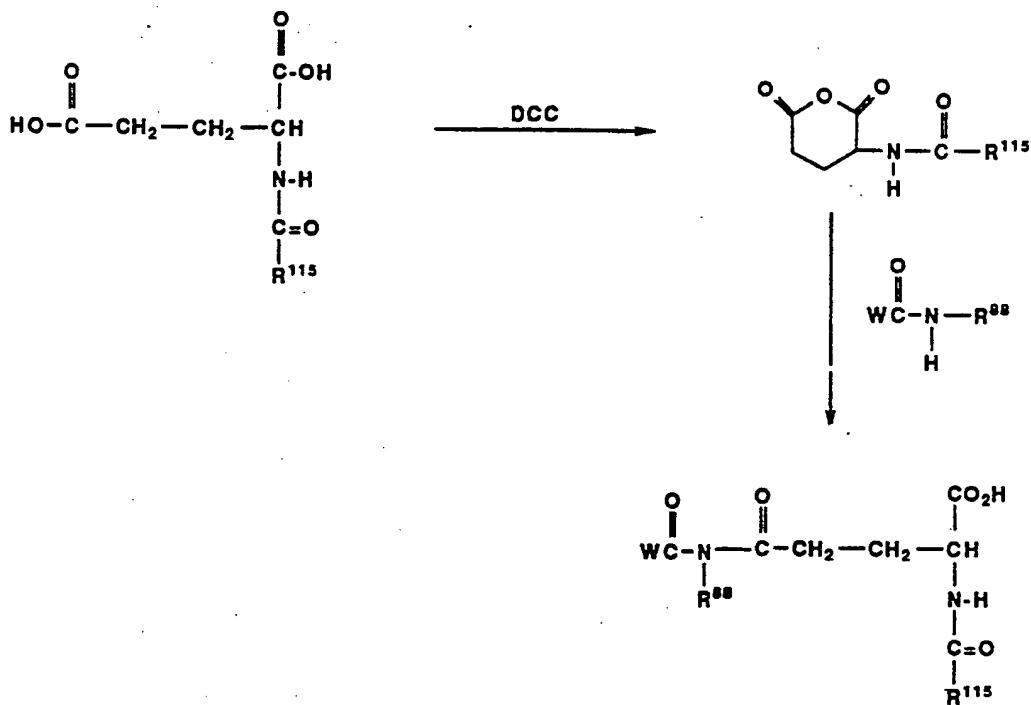
amino-containing precursor for synthesizing a conjugate of the invention. In the following General Synthetic Procedures, the substituents and reagents are defined as follows: each of R⁷⁹, R⁸⁰, R⁸¹, R⁸⁶, R⁸⁷, R⁸⁸, R⁸⁹ and 5 R¹¹⁵ is as defined above; W is selected from alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl; and Z is selected from oxygen and sulfur. DCC is an abbreviation for dicyclohexylcarbodiimide.

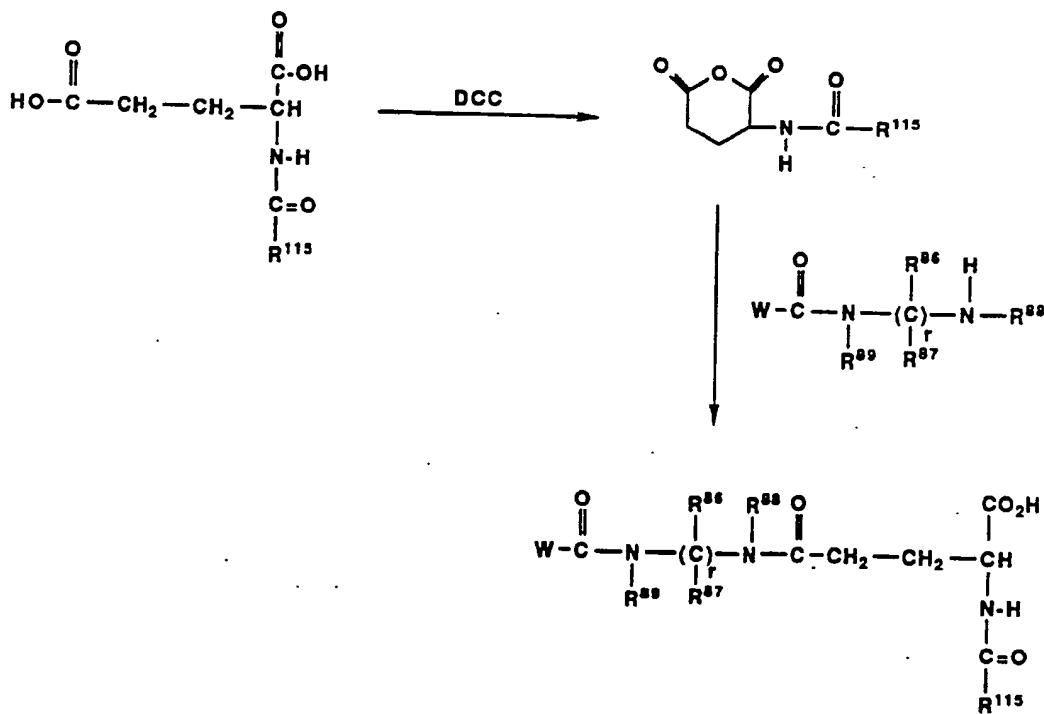
General Synthetic ProceduresProcedure 1:

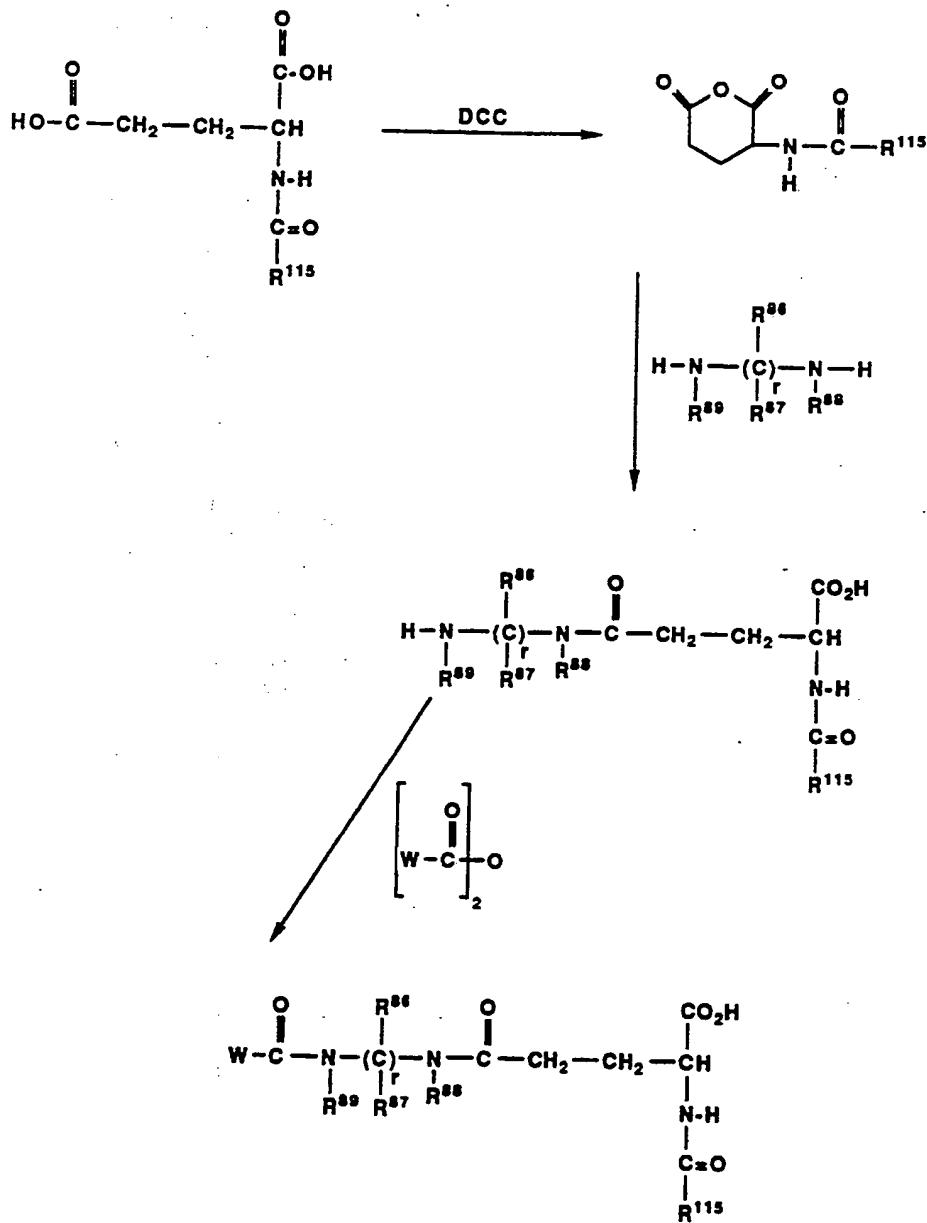
Procedure 2:

Procedure 3:

Procedure 4:

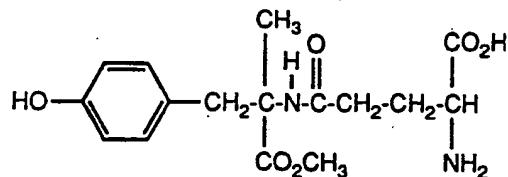
Procedure 5:

Procedure 6:

Procedure 7:

The following Examples 1-1857 shown in Tables IV-XVII are highly preferred conjugates of the invention. These conjugates fall within three classes, namely, conjugates of tyrosine hydroxylase inhibitors of Tables IV-VI, conjugates of 5 dopa-decarboxylase inhibitors of Tables VII-XI, and conjugates of dopamine- β -hydroxylase inhibitors of Tables XII-XVII. These conjugates may be prepared generally by the procedures outlined above in Schemes 1-7. Also, specific procedures for preparation of Examples 1-1857 are found in the conjugate 10 preparations described in the examples appearing with the tables of conjugates.

The following Examples #1-#461 comprise three classes of highly preferred conjugates formed from tyrosine 15 hydroxylase inhibitor compounds and glutamic acid derivatives. Examples #1-#3 are descriptions of specific preparations of such conjugates. Examples #4-#461, as shown in Tables IV-VI, may be prepared by procedures shown in these specific examples and in the foregoing general synthetic procedures of Schemes 20 1-7.

Example 1

5

4-amino-4-carboxy-4-oxobutyl-alpha-methyl-L-tyrosine, methyl ester.

10

Step. 1. Preparation of methyl alpha-methyl-L-tyrosinate, hydrochloride.

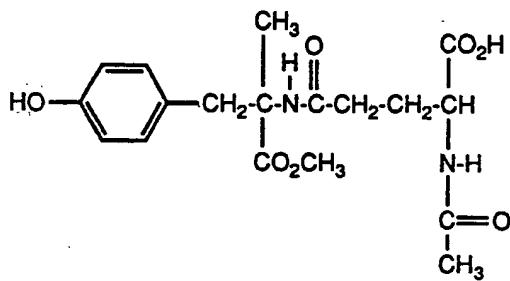
A solution of 11.0 g (56.4 mmol) of α -methyl-L-tyrosine in 100 mL of absolute methanol was cooled to 0°C and treated with 20.1 g (169 mmol) of thionyl chloride under a nitrogen atmosphere. The reaction was allowed to warm to ambient temperature and stir at reflux for 2 days.

Concentration followed by trituration with 150 mL of ether gave 13.3 g (96%) of colorless product: NMR (DMSO-d₆) δ 1.49 (s, 3H), 3.02 (s, 2H), 3.73 (s, 3H), 6.73 (d, J = 11 Hz, 2H), 6.97 (d, J = 11 Hz, 2H), 8.50-8.70 (br s, 3H), 9.50 (s, 1H).

Step. 2. Preparation of 4-amino-4-carboxy-4-oxobutyl-alpha-methyl-L-tyrosine, methyl ester.

Under nitrogen, a solution of 35.1 g (116 mmol) of N-Boc-L-γ-glutamic acid-α-t-butyl ester (BACHEM) in 200 mL of methylene chloride was treated with 11.95 g (58 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction was allowed to stir for 2 hr prior to filtration under a nitrogen atmosphere. The methylene chloride was removed in vacuo and the residue

dissolved in 100 mL of anhydrous dimethylformamide (DMF). The anhydride solution was slowly added to a solution of 7.0 g (29 mmol) of the α -methyl tyrosine ester from step 1 and 18.73 g (145 mmol) of diisopropylethylamine (DIEA) in 100 mL of
5 anhydrous DMF. The reaction was allowed to stir overnight and was concentrated in vacuo. The residue was dissolved in ethyl acetate, washed with cold 1M K₂CO₃ followed by water, dried (MgSO₄), and concentrated in vacuo to give the protected coupled product; a solution of this material in 150 mL of
10 methylene chloride was cooled to 0°C and treated with 150 mL of trifluoracetic acid (TFA) under nitrogen. The reaction was allowed to warm to ambient temperatures and stir overnight. Concentration in vacuo gave 4-amino-4-carboxy-4-oxobutyl- α -methyl-L-tyrosine, methyl ester: NMR (DMSO-d₆) δ 1.20 (s,
15 3H), 1.90-2.20 (m, 2H), 2.23-2.38 (m, 2H), 2.95 (d, J = 13 Hz, 1H), 3.26 (d, J = 13 Hz), 3.57 (s, 3H), 3.92-4.06 (m, 1H), 7.06 (d, J = 9 Hz, 2H), 7.12 (d, J = 9 Hz, 2H).

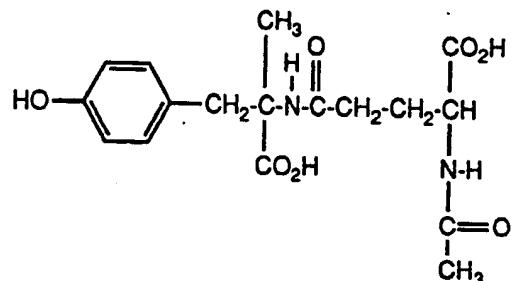
Example 2

5

N-[4-(acetylamino)-4-carboxy-4-oxobutyl]-α-methyl-L-tyrosine, methyl ester.

10 The compound of Example 1 was dissolved in 100 mL of water and the pH adjusted to 9 with 1 M K₂CO₃. The solution was cooled to 0°C and 3.30 mL (35 mmol) of acetic anhydride and 35 mL (35 mmol) of 1 M K₂CO₃ was added every 30 min. for 5 h; the pH was maintained at 9 and the reaction 15 temperature kept below 5°C. After the last addition, the reaction was allowed to warm to ambient temperature overnight. The pH was adjusted to 4 with 6 M HCl and concentrated to 100 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) using isocratic 25% acetonitrile/water (0.05% 20 TFA) gave 9.0 g (82%) of colorless product: NMR (DMSO-d₆) δ 1.18 (s, 3H), 1.72-2.03 (m, 2H), 1.85 (s, 3H), 2.15 (t, J = 8 Hz, 2H), 2.93 (d, J = 13 Hz, 1H), 3.38 (d, J = 13 Hz, 1H), 3.57 (s, 3H), 4.12-4.23 (m, 1H), 7.02 (d, J = 9 Hz, 2H), 7.09 (d, J = 9 Hz, 2H), 8.06 (s, 1H), 8.12 (d, J = 8 Hz, 1H).

25

Example 3

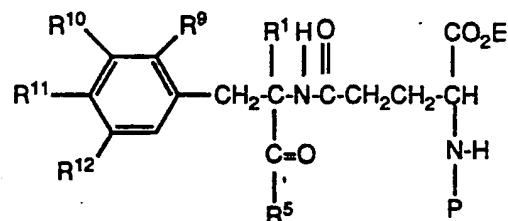
5

N-[4-(acetylamino)-4-carboxy-4-oxobutyl]-α-methyl-L-tyrosine.

A solution of 9.0 g (23.7 mmol) of the compound of
 10 Example 2 in 225 mL of water was cooled to 0°C and treated
 with 3.3 g (82.5 mmol) of solid NaOH in portions over 15 min.
 The reaction was stirred at 0-5°C overnight, the pH adjusted
 to pH 5 with 6N HCl, and concentrated to 100 mL. Purification
 by reverse phase chromatography (Waters Deltaprep-3000) using
 15 isocratic 15% acetonitrile/water (0.05% TFA) gave 5.50 g (63%)
 of colorless product: NMR (DMSO-d₆) δ 1.17 (s, 3H), 1.70-2.00
 (m, 2H), 1.85 (s, 3H), 2.14 (t, J = 8 Hz, 2H), 2.83 (d, J = 13
 Hz, 1H), 3.14 (d, J = 13 Hz, 1H), 4.12-4.23 (m, 1H), 6.56 (d,
 J = 9 Hz, 2H), 6.85 (d, J = 9 Hz, 2H), 7.69 (s, 1H), 8.12 (d,
 20 J = 8 Hz, 1H); MS (FAB) m/e (rel intensity) 367 (70), 196
 (52), 179 (58) 150 (100), 130 (80); HRMS. Calcd for M + H:
 367.1505. Found: 367.1547. Anal. Calcd for
 C₁₇H₂₂N₂O₇•H₂O•0.125 TFA: C, 52.00; H, 6.03; N, 7.03; F,
 1.60. Found: C, 51.96; H, 6.25; N, 7.12; F, 1.60.

25

The following Examples #4-#109 of Table IV are
 highly preferred conjugates formed from tyrosine hydroxylase
 inhibitor compounds and glutamic acid derivatives. These
 30 tyrosine hydroxylase inhibitors utilized to make these
 conjugates are embraced by generic Formula I and II, above.

TABLE IV

EXAMPLE NO.	R ¹	R ⁹	R ¹⁰	R ¹¹	R ¹²	R ⁵	E	P
4	CH ₃	H	H	OH	H	OCH ₃	CH ₃	COCH ₃
5	CH ₃	H	H	OH	H	OH	H	H
6	CH ₃	H	H	OH	H	OCH ₃	CH ₃	H
7	CH ₃	H	H	OH	H	OH	CH ₃	H
8	CH ₃	H	H	OH	H	OH	CH ₃	COCH ₃
9	CH ₂ F	H	H	OH	H	OCH ₃	H	H
10	CH ₂ F	H	H	OH	H	OCH ₃	H	COCH ₃
11	CH ₂ F	H	H	OH	H	OCH ₃	CH ₃	H
12	CH ₂ F	H	H	OH	H	OCH ₃	CH ₃	COCH ₃
13	CH ₂ F	H	H	OH	H	OH	H	H
14	CH ₂ F	H	H	OH	H	OH	H	COCH ₃

EXAMPLE NO.	R ¹	R ⁹	R ¹⁰	R ¹¹	R ¹²	R ⁵	E	P
15	CH ₂ F	H	H	OH	H	OH	CH ₃	H
16	CH ₂ F	H	H	OH	H	OH	CH ₃	COCH ₃
17	CHF ₂	H	H	OH	H	OCH ₃	H	H
18	CHF ₂	H	H	OH	H	OCH ₃	H	COCH ₃
19	CHF ₂	H	H	OH	H	OCH ₃	CH ₃	H
20	CHF ₂	H	H	OH	H	OCH ₃	CH ₃	COCH ₃
21	CHF ₂	H	H	OH	H	OH	H	H
22	CHF ₂	H	H	OH	H	OH	H	COCH ₃
23	CHF ₂	H	H	OH	H	OH	CH ₃	H
24	CHF ₂	H	H	OH	H	OH	CH ₃	COCH ₃
25	CF ₃	H	H	OH	H	OCH ₃	H	H
26	CF ₃	H	H	OH	H	OCH ₃	H	COCH ₃
27	CF ₃	H	H	OH	H	OCH ₃	CH ₃	H
28	CF ₃	H	H	OH	H	OCH ₃	CH ₃	COCH ₃
29	CF ₃	H	H	OH	H	OH	H	H
30	CF ₃	H	H	OH	H	OH	H	COCH ₃

EXAMPLE NO.	R ¹	R ⁹	R ¹⁰	R ¹¹	R ¹²	R ⁵	E	P
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31	CF ₃	H	H	OH	H	OH	CH ₃	H
32	CF ₃	H	H	OH	H	OH	CH ₃	COCH ₃
33	C ₂ H ₅	H	H	OH	H	OCH ₃	H	H
34	C ₂ H ₅	H	H	OH	H	OCH ₃	H	COCH ₃
35	C ₂ H ₅	H	H	OH	H	OCH ₃	CH ₃	H
36	C ₂ H ₅	H	H	OH	H	OCH ₃	CH ₃	COCH ₃
37	C ₂ H ₅	H	H	OH	H	OH	H	H
38	C ₂ H ₅	H	H	OH	H	OH	H	COCH ₃
39	C ₂ H ₅	H	H	OH	H	OH	CH ₃	H
40	C ₂ H ₅	H	H	OH	H	OH	CH ₃	COCH ₃
41	C ₃ H ₇	H	H	OH	H	OCH ₃	H	H
42	C ₃ H ₇	H	H	OH	H	OCH ₃	H	COCH ₃
43	C ₃ H ₇	H	H	OH	H	OCH ₃	CH ₃	H
44	C ₃ H ₇	H	H	OH	H	OCH ₃	CH ₃	COCH ₃
45	C ₃ H ₇	H	H	OH	H	OH	H	H

EXAMPLE NO.	R ¹	R ⁹	R ¹⁰	R ¹¹	R ¹²	R ⁵	E	P
46	C ₃ H ₇	H	H	OH	H	OH	H	COCH ₃
47	C ₃ H ₇	H	H	OH	H	OH	CH ₃	H
48	C ₃ H ₇	H	H	OH	H	OH	CH ₃	COCH ₃
49	CH ₃	H	H	NHCN	H	OH	H	COCH ₃
50	CH ₃	H	CO ₂ H	H	H	H	OH	COCH ₃
51	CH ₃	H	CN	H	H	OH	H	COCH ₃
52	CH ₃	H	H	CH ₂ NH ₂	H	OH	H	COCH ₃
53	CH ₃	H	H	CH ₂ CH ₂ CN	H	OH	H	COCH ₃
54	CH ₃	H	OH	CH ₃ SO ₂ NH	H	OH	H	COCH ₃
55	CH ₃	H	OH	NO ₂	H	OH	H	COCH ₃
56	CH ₃	H	CH ₃ SO ₃	NH ₂	H	OH	H	COCH ₃
57	CH ₃	H	CO ₂ CH ₃	NO ₂	H	OH	H	COCH ₃
58	CH ₃	H	NO ₂	NH ₂	H	OH	H	COCH ₃
59	CH ₃	H	NH ₂	NH ₂	H	OH	H	COCH ₃
60	CH ₃	H	CH ₃	OH	H	OH	H	COCH ₃

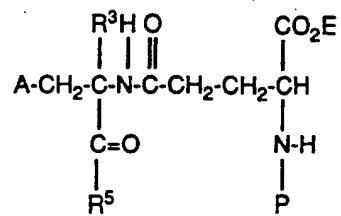
EXAMPLE NO.	R ¹	R ⁹	R ¹⁰	R ¹¹	R ¹²	R ⁵	E	P
61	CH ₃	H	C ₆ H ₅	OH	H	OH	H	COCH ₃
62	CH ₃	H	CH ₂ C ₆ H ₅	OH	H	OH	H	COCH ₃
63	CH ₃	H	C ₆ H ₁₁ (cyclo)	CH ₃ O	H	OH	H	COCH ₃
64	CH ₃	OH	OH	H	H	OH	H	COCH ₃
65	CH ₃	OH	OH	Cl	H	OH	H	COCH ₃
66	CH ₃	OH	OH	CH ₃	H	OH	H	COCH ₃
67	CH ₃	OH	OH	F	H	OH	H	COCH ₃
68	CH ₃	OH	OH	CF ₃	H	OH	H	COCH ₃
69	CH ₃	H	OH	H	OH	OH	H	COCH ₃
70	CH ₃	H	OH	Cl	OH	OH	H	COCH ₃
71	CH ₃	H	OH	F	OH	OH	H	COCH ₃
72	CH ₃	H	OH	CF ₃	OH	OH	H	COCH ₃
73	CH ₃	OH	H	H	OH	OH	H	COCH ₃
74	CH ₃	OH	H	Cl	OH	OH	H	COCH ₃
75	CH ₃	OH	H	CH ₃	OH	OH	H	COCH ₃
76	CH ₃	OH	H	CF ₃	OH	OH	H	COCH ₃

EXAMPLE NO.	R ¹	R ⁹	R ¹⁰	R ¹¹	R ¹²	R ⁵	E	P
77	CH ₃	H	OH	OH	OH	OH	H	COCH ₃
78	CH ₃	OH	OH	OH	H	OH	H	COCH ₃
79	CH ₃	OH	H	OH	OH	OH	H	COCH ₃
80	CH ₃	H	H	H	H	OH	H	COCH ₃
81	H	H	H	H	H	OH	H	COCH ₃
82	H	H	I	H	H	H	H	COCH ₃
83	CH ₃	H	I	H	H	H	H	COCH ₃
84	H	H	I	OH	H	H	H	COCH ₃
85	H	H	I	H	I	H	H	COCH ₃
86	CH ₃	H	CH ₃	OH	H	H	H	COCH ₃
87	CH ₃	H	C ₆ H ₅ CH ₂	CH ₃ O	H	H	H	COCH ₃
88	CH ₃	H	C ₆ H ₅ CH ₂	OH	H	H	H	COCH ₃
89	CH ₃	H	C ₆ H ₁₁ (cyclo)	CH ₃ O	H	H	H	COCH ₃
90	CH ₃	H	C ₆ H ₁₁ (cyclo)	OH	H	H	H	COCH ₃
91	CH ₃	H	CH ₃	CH ₃ O	H	H	H	COCH ₃

EXAMPLE NO.	R ¹	R ⁹	R ¹⁰	R ¹¹	R ¹²	R ⁵	E	P
92	CH ₃	H	CH ₃	OH	H	H	H	COCH ₃
93	CH ₃	H	CH ₃ C ₆ H ₅ CH ₂ CO ₂	H	H	H	H	COCH ₃
94	CH ₃	H	CH ₃	OH	H	H	H	COCH ₃
95	CH ₃	H	CH ₃ C ₆ H ₅ CH ₂ CO ₂	H	H	H	H	COCH ₃
96	CH ₃	H	CH ₃	CH ₃ CO ₂	H	H	H	COCH ₃
97	CH ₃	H	CH ₃ O	OH	H	H	H	COCH ₃
98	CH ₃	H	-OCH ₂ O-		H	H	H	COCH ₃
99	CH ₃	CH ₃ O	H	H	CH ₃ O	H	H	COCH ₃
100	CH ₃	OH	H	H	OH	H	H	COCH ₃
101	CH ₃	CH ₃ O	H	CH ₃ O	H	H	H	COCH ₃
102	CH ₃	OH	H	OH	H	H	H	COCH ₃
103	CH ₃	CH ₃ O	H	H	CH ₃ O OC ₂ H ₅	H	H	COCH ₃
104	C=CH	CH ₃ O	H	H	H	H	H	COCH ₃
105	C=CH	CH ₃ O	H	H	CH ₃ O	H	H	COCH ₃
106	C=CH	H	H	OH	H	H	H	COCH ₃

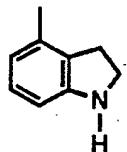
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107	C = CH	H	OH	H	H	H	H	COCH ₃
108	CH = CH ₂	CH ₃ O	H	H	H	H	H	COCH ₃
109	CH = CH ₂	CH ₃ O	H	H	CH ₃ O	H	H	COCH ₃

The following Examples #110-#413 of Table V are highly preferred conjugates formed from tyrosine hydroxylase inhibitor compounds and glutamic acid derivatives. These tyrosine hydroxylase inhibitors utilized to make these conjugates are embraced by generic Formula I, above.

TABLE V

EXAMPLE NO.	A	R ³	R ⁵	E	P
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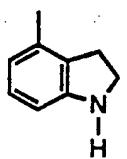
110

CH₃OCH₃

H

H

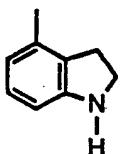
111

CH₃OCH₃

H

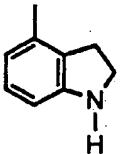
COCH₃

112

CH₃OCH₃CH₃

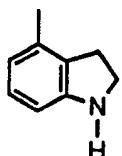
H

113

CH₃OCH₃CH₃COCH₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
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114

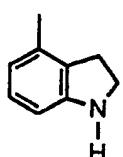
CH₃

OH

H

H

115

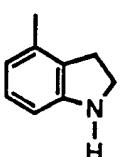
CH₃

OH

H

COCH₃

116

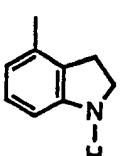
CH₃

OH

CH₃

H

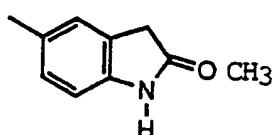
117

CH₃

OH

CH₃COCH₃

118

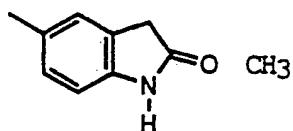
OCH₃

H

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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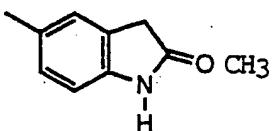
119

CH₃OCH₃

H

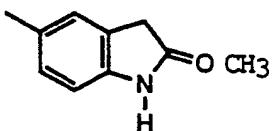
COCH₃

120

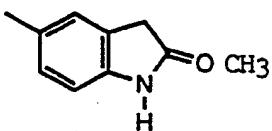
CH₃OCH₃CH₃

H

121

CH₃OCH₃CH₃COCH₃

122

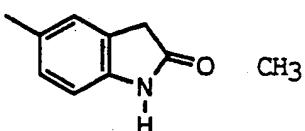
CH₃

OH

H

H

123

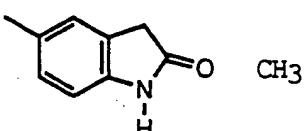
CH₃

OH

H

COCH₃

124

CH₃

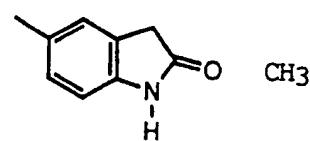
OH

CH₃

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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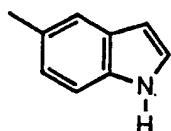
125

CH₃

OH

CH₃COCH₃

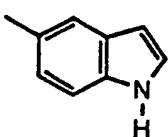
126

CH₃OCH₃

H

H

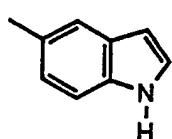
127

CH₃OCH₃

H

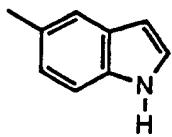
COCH₃

128

CH₃OCH₃CH₃

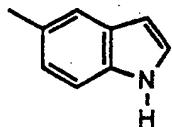
H

129

CH₃OCH₃CH₃COCH₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
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130

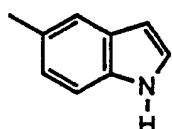
CH₃

OH

H

H

131

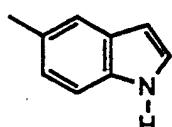
CH₃

OH

H

COCH₃

132

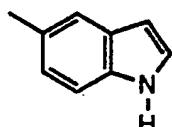
CH₃

OH

CH₃

H

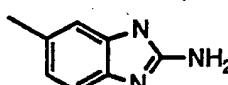
133

CH₃

OH

CH₃COCH₃

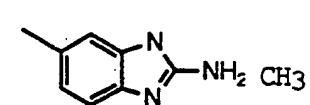
134

CH₃OCH₃

H

H

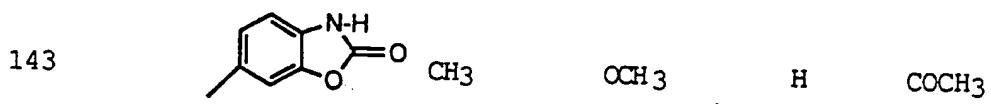
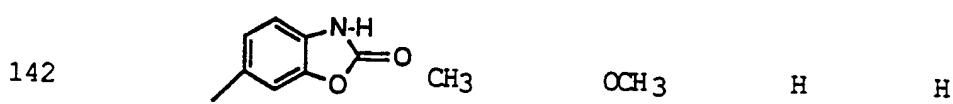
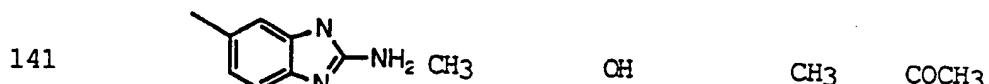
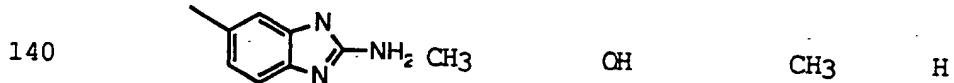
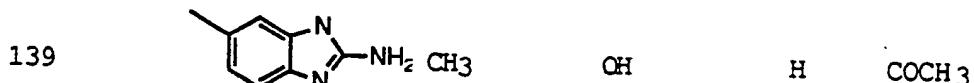
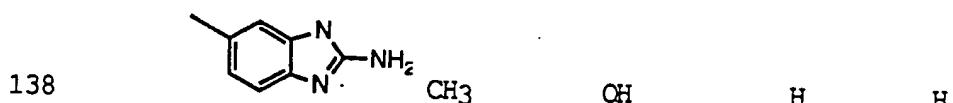
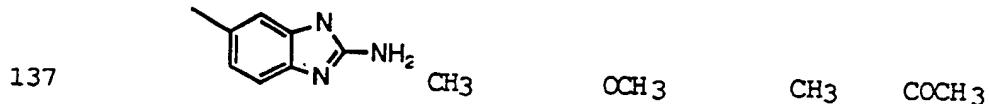
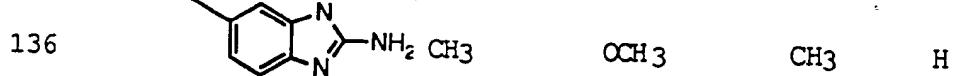
135

CH₃OCH₃

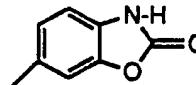
H

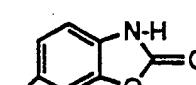
COCH₃

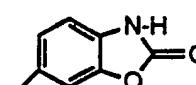
EXAMPLE NO.	A	R ³	R ⁵	E	P
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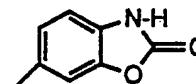


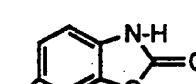
EXAMPLE NO.	A	R ³	R ⁵	E	P
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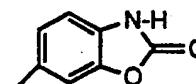
144  CH₃ OCH₃ CH₃ H

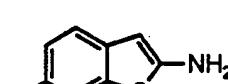
145  CH₃ OCH₃ CH₃ COCH₃

146  CH₃ OH H H

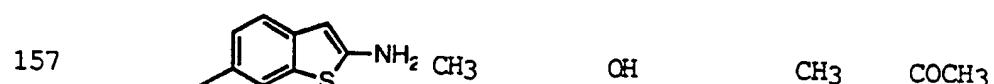
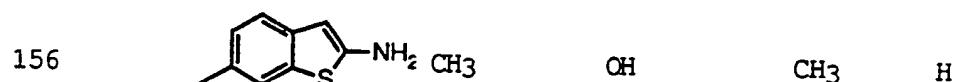
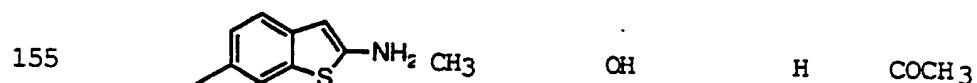
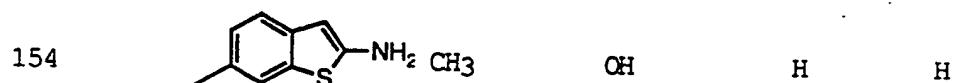
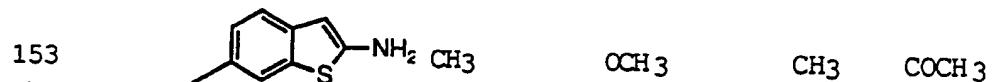
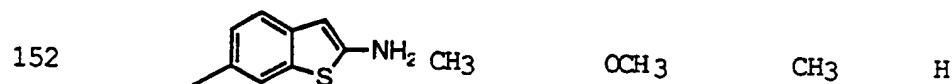
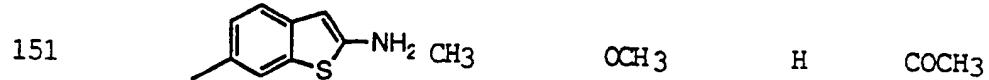
147  CH₃ OH H COCH₃

148  CH₃ OH CH₃ H

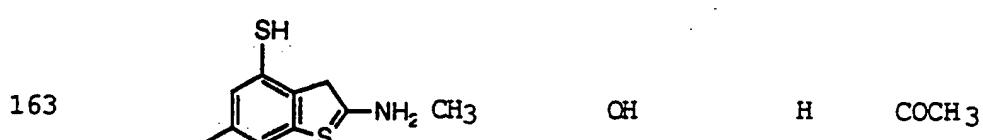
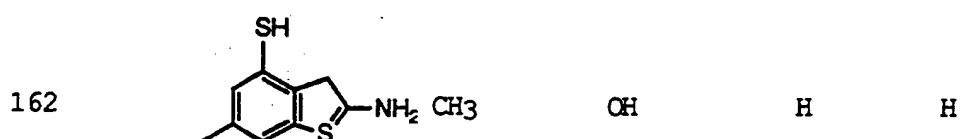
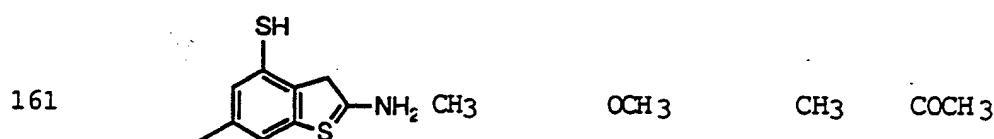
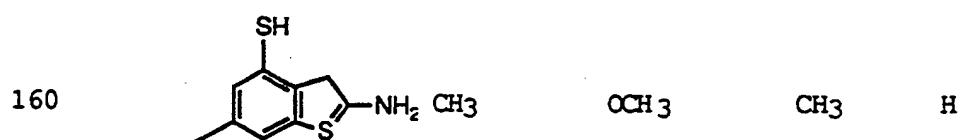
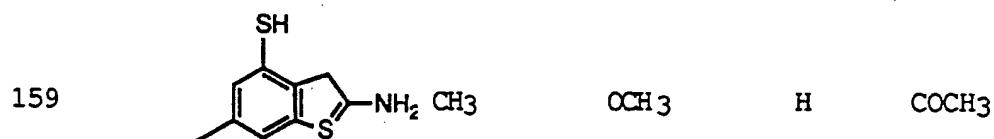
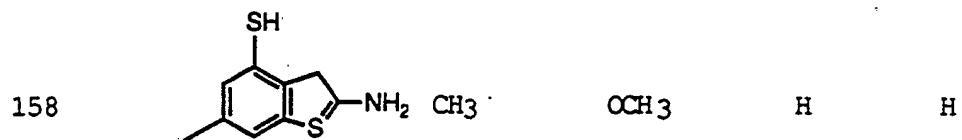
149  CH₃ OH CH₃ COCH₃

150  NH₂ CH₃ OCH₃ H H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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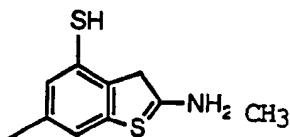


EXAMPLE NO.	A	R ³	R ⁵	E	P
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EXAMPLE NO.	A	R ³	R ⁵	E	P
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164

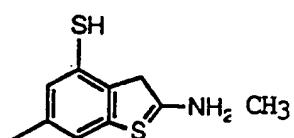


OH

CH₃

H

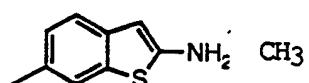
165



OH

CH₃COCH₃

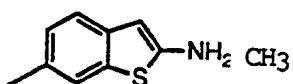
166

OCH₃

H

H

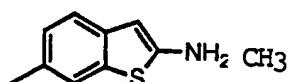
167

OCH₃

H

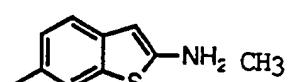
COCH₃

168

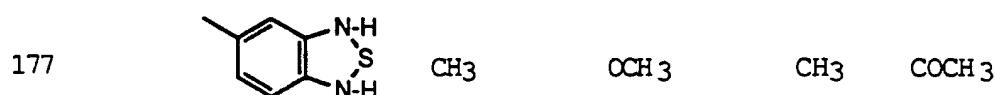
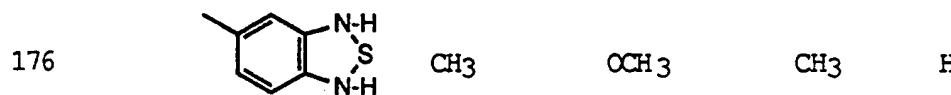
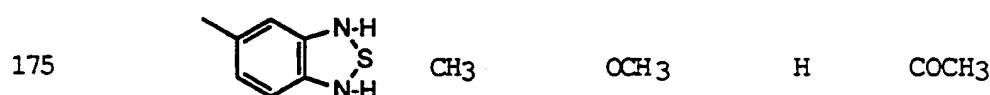
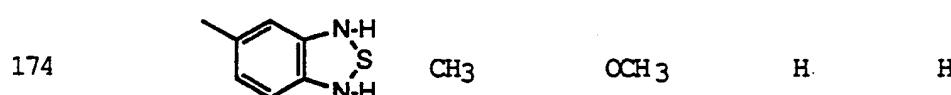
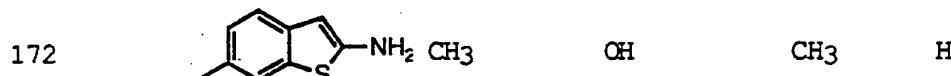
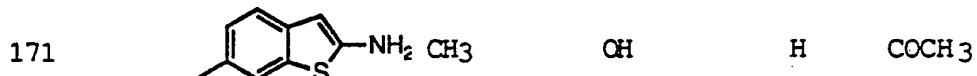
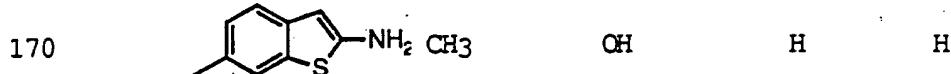
OCH₃CH₃

H

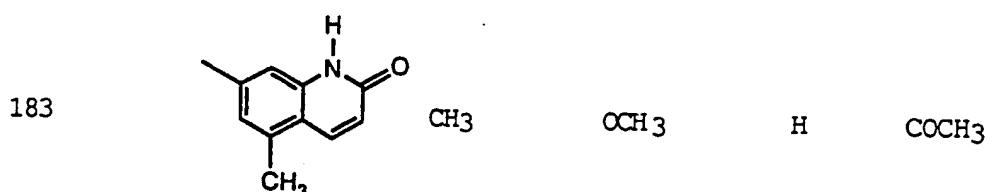
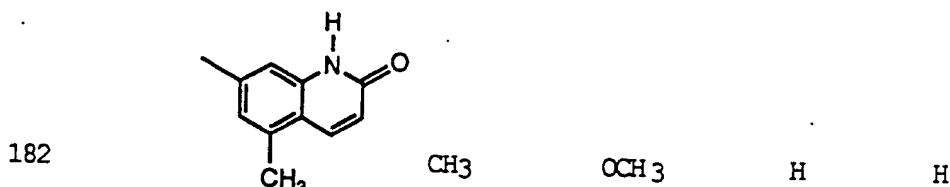
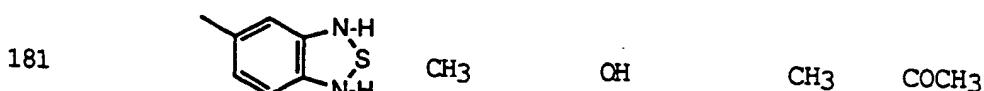
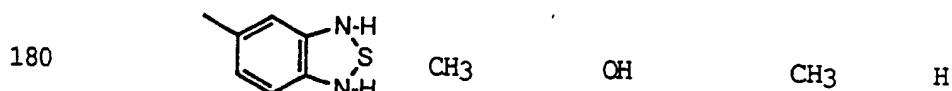
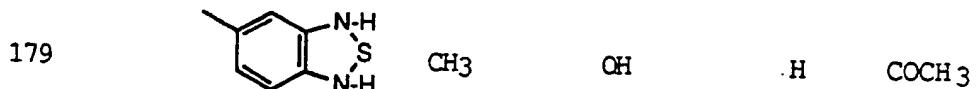
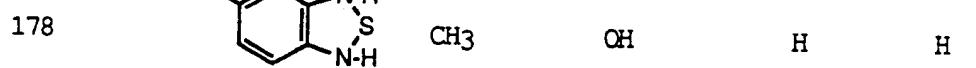
169

OCH₃CH₃COCH₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
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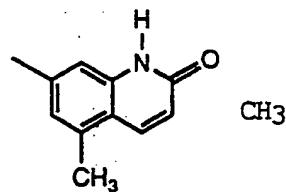


EXAMPLE NO.	A	R ³	R ⁵	E	P
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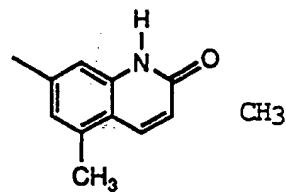
EXAMPLE NO.	A	R ³	R ⁵	E	P
----------------	---	----------------	----------------	---	---

184

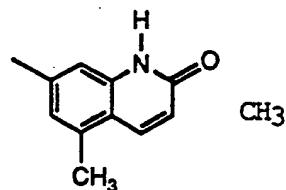
CH₃OCH₃CH₃

H

185

CH₃OCH₃CH₃COCH₃

186

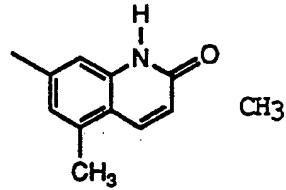
CH₃

OH

H

H

187

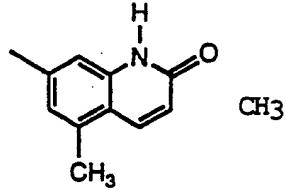
CH₃

OH

H

COCH₃

188

CH₃

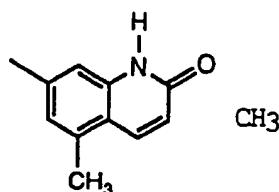
OH

CH₃

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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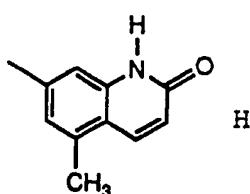
189

CH₃

OH

CH₃COCH₃

190



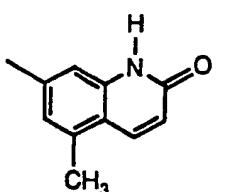
H

OCH₃

H

H

191



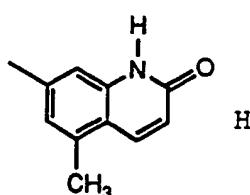
H

OCH₃

H

COCH₃

192



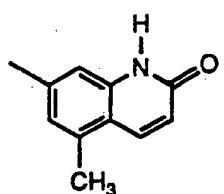
H

OCH₃CH₃

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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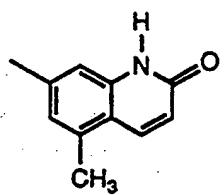
193



H

OCH₃CH₃COCH₃

194



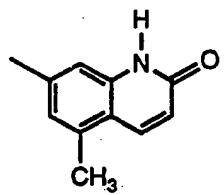
H

OH

H

H

195



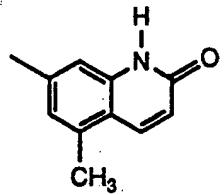
H

OH

H

COCH₃

196



H

OH

CH₃

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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197

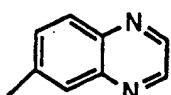


H

OH

CH₃COCH₃

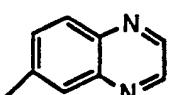
198

CH₃OCH₃

H

H

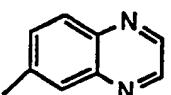
199

CH₃OCH₃

H

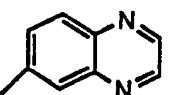
COCH₃

200

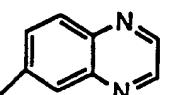
CH₃OCH₃CH₃

H

201

CH₃OCH₃CH₃COCH₃

202

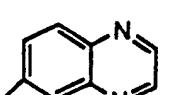
CH₃

OH

H

H

203

CH₃

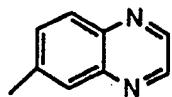
OH

H

COCH₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
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204

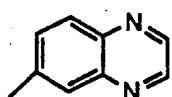
CH₃

OH

CH₃

H

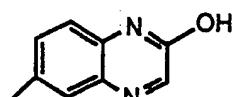
205

CH₃

OH

CH₃COCH₃

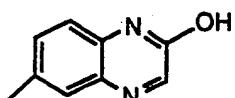
206

CH₃OCH₃

H

H

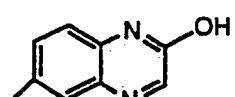
207

CH₃OCH₃

H

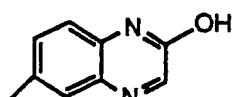
COCH₃

208

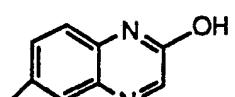
CH₃OCH₃CH₃

H

209

CH₃OCH₃CH₃COCH₃

210

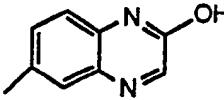
CH₃

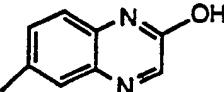
OH

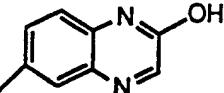
H

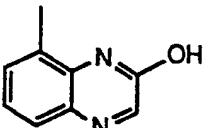
H

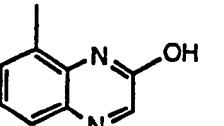
EXAMPLE NO.	A	R ³	R ⁵	E	P
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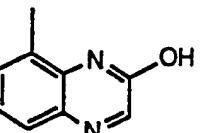
211  CH₃ OH H COCH₃

212  CH₃ OH CH₃ H

213  CH₃ OH CH₃ COCH₃

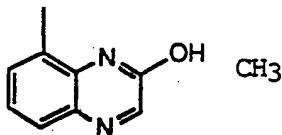
214  CH₃ OCH₃ H H

215  CH₃ OCH₃ H COCH₃

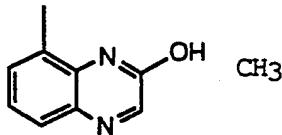
216  CH₃ OCH₃ CH₃ H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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217

CH₃OCH₃CH₃COCH₃

218

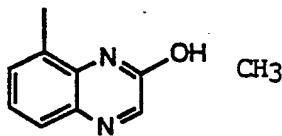
CH₃

OH

H

H

219

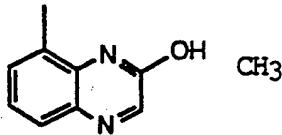
CH₃

OH

H

COCH₃

220

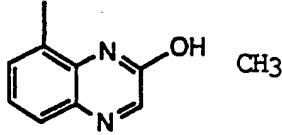
CH₃

OH

CH₃

H

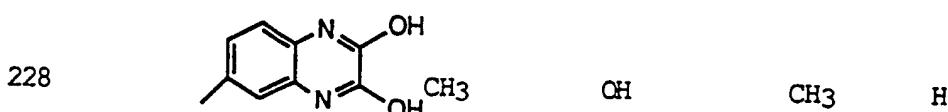
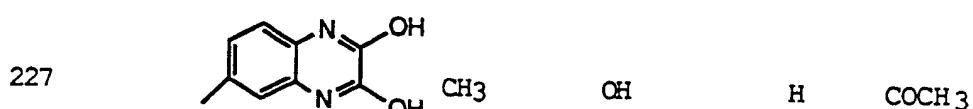
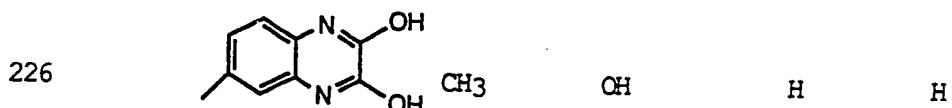
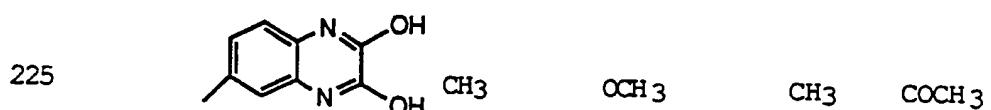
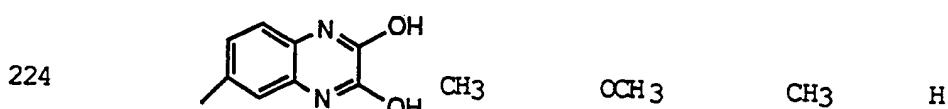
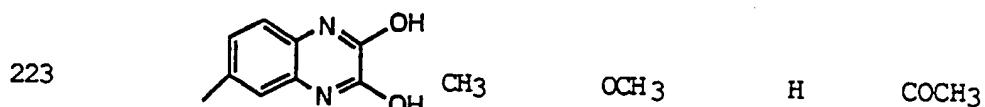
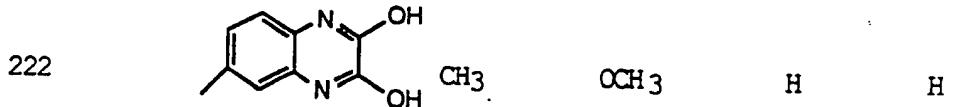
221

CH₃

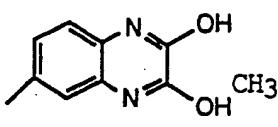
OH

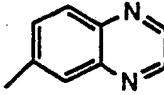
CH₃COCH₃

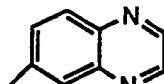
EXAMPLE NO.	A	R ³	R ⁵	E	P
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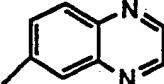


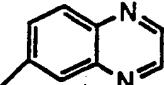
EXAMPLE NO.	A	R ³	R ⁵	E	P
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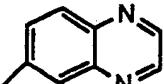
229  OH CH₃ COCH₃

230  H OCH₃ H H

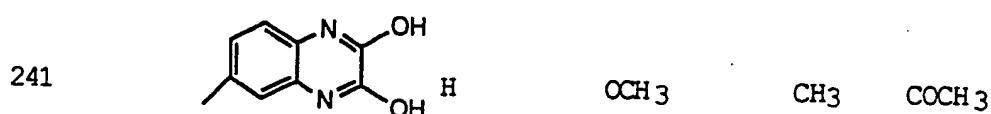
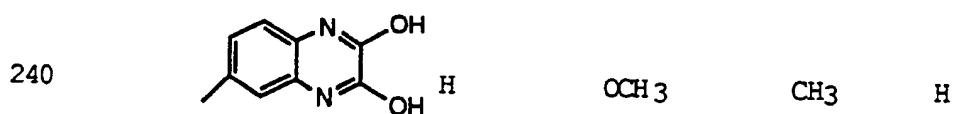
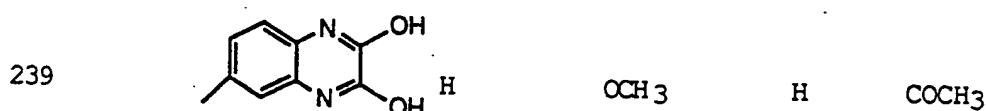
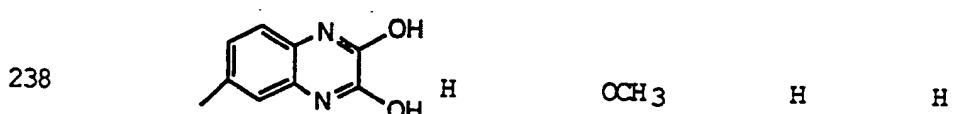
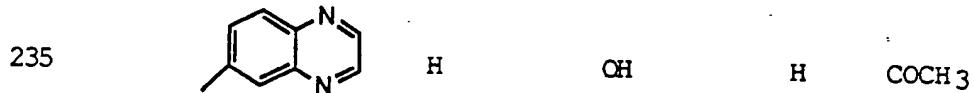
231  H OCH₃ H COCH₃

232  H OCH₃ CH₃ H

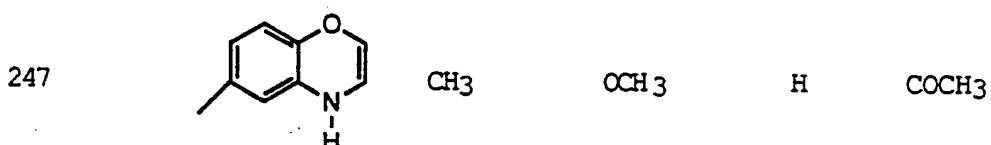
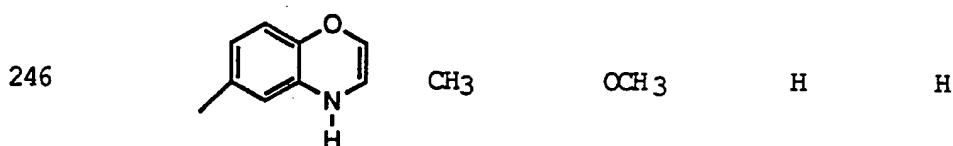
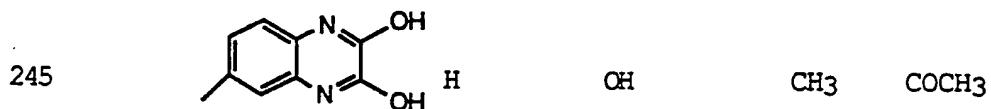
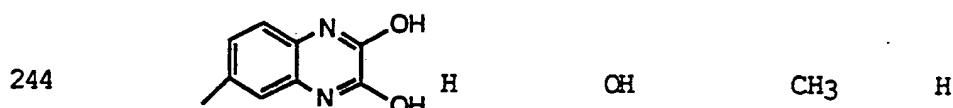
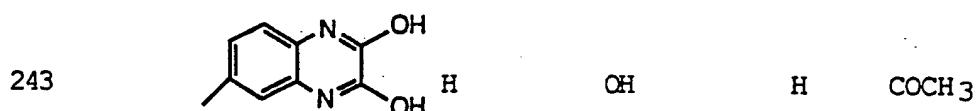
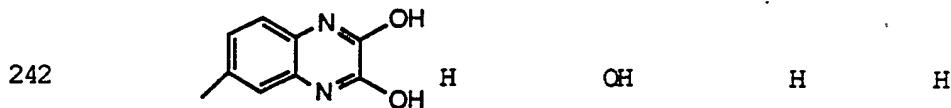
233  H OCH₃ CH₃ COCH₃

234  H OH H H

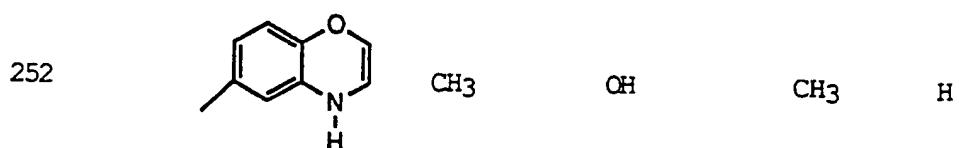
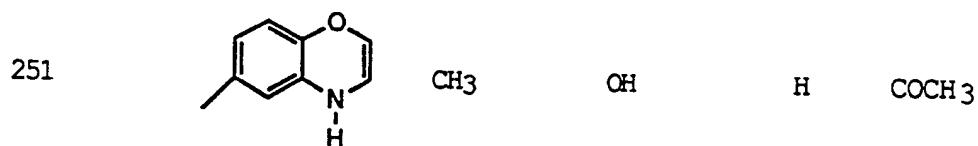
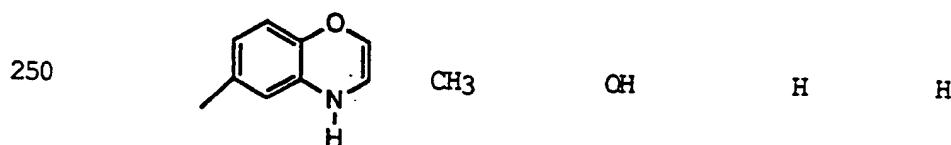
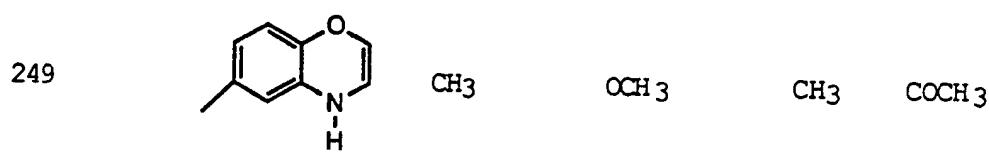
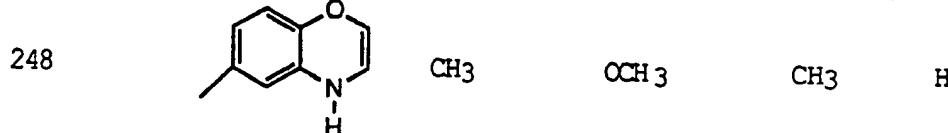
EXAMPLE NO.	A	R ³	R ⁵	E	P
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EXAMPLE NO.	A	R ³	R ⁵	E	P
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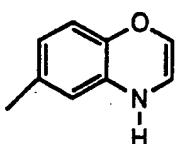


EXAMPLE NO.	A	R ³	R ⁵	E	P
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EXAMPLE NO.	A	R ³	R ⁵	E	P
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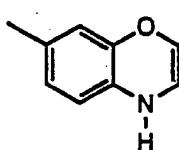
253

CH₃

OH

CH₃COCH₃

254



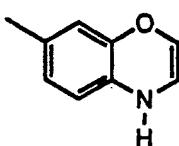
H

OCH₃

H

H

255



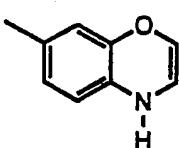
H

OCH₃

H

COCH₃

256

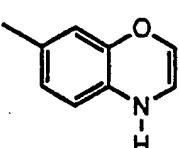


H

OCH₃CH₃

H

257

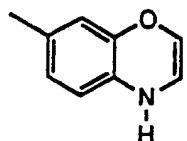


H

OCH₃CH₃COCH₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
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258



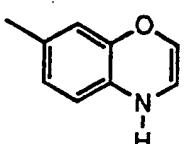
H

OH

H

H

259



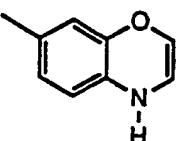
H

OH

H

COCH₃

260



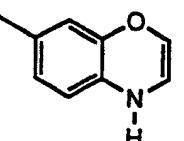
H

OH

CH₃

H

261

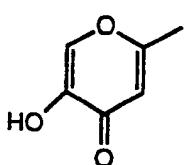


H

OH

CH₃COCH₃

262

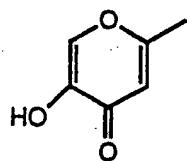
CH₃OCH₃

H

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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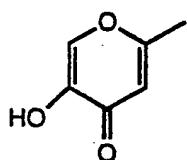
263

CH₃OCH₃

H

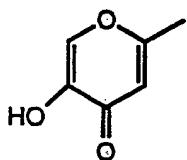
COCH₃

264

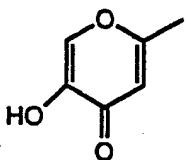
CH₃OCH₃CH₃

H

265

CH₃OCH₃CH₃COCH₃

266

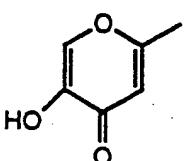
CH₃

OH

H

H

267

CH₃

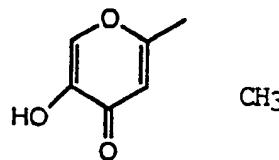
OH

H

COCH₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
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268

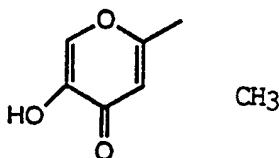
CH₃

OH

CH₃

H

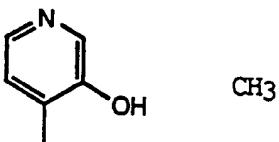
269

CH₃

OH

CH₃COCH₃

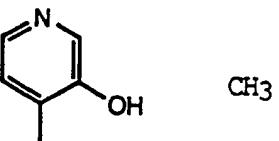
270

CH₃OCH₃

H

H

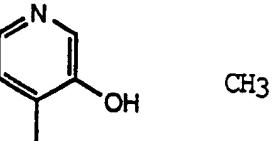
271

CH₃OCH₃

H

COCH₃

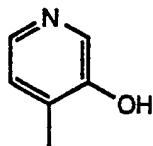
272

CH₃OCH₃CH₃

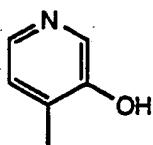
H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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273

CH₃OCH₃CH₃COCH₃

274

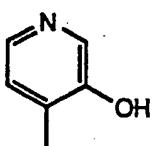
CH₃

OH

H

H

275

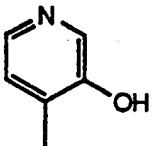
CH₃

OH

H

COCH₃

276

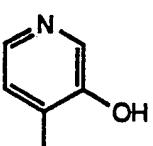
CH₃

OH

CH₃

H

277

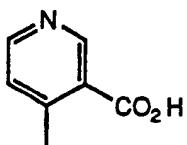
CH₃

OH

CH₃COCH₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
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278



A

R³R⁵

E

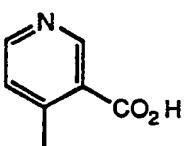
P

CH₃OCH₃

H

H

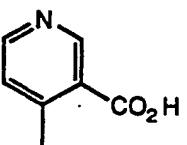
279

CH₃OCH₃

H

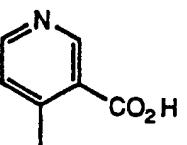
COCH₃

280

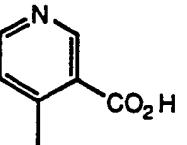
CH₃OCH₃CH₃

H

281

CH₃OCH₃CH₃COCH₃

282

CH₃

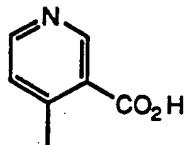
OH

H

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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283

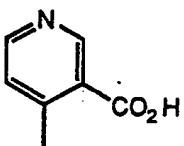
CH₃

OH

H

COCH₃

284

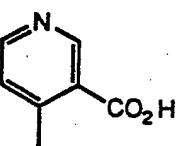
CH₃

OH

CH₃

H

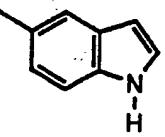
285

CH₃

OH

CH₃COCH₃

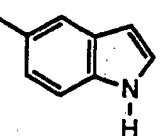
286

CH₃OCH₃

H

H

287

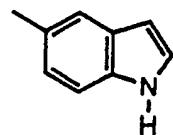
CH₃OCH₃

H

COCH₃

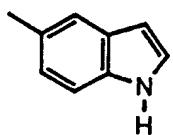
EXAMPLE NO.	A	R ³	R ⁵	E	P
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288

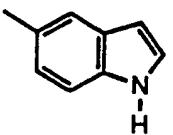
CH₃OCH₃CH₃

H

289

CH₃OCH₃CH₃COCH₃

290

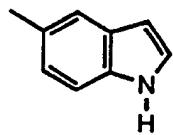
CH₃

OH

H

H

291

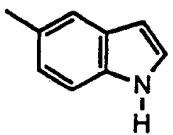
CH₃

OH

H

COCH₃

292

CH₃

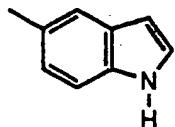
OH

CH₃

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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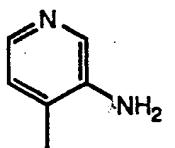
293

CH₃

OH

CH₃COCH₃

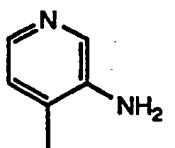
294

CH₃OCH₃

H

H

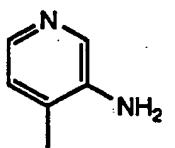
295

CH₃OCH₃

H

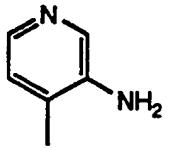
COCH₃

296

CH₃OCH₃CH₃

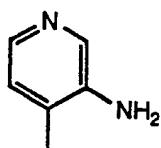
H

297

CH₃OCH₃CH₃COCH₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
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298

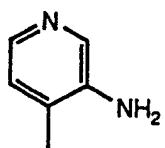
CH₃

OH

H

H

299

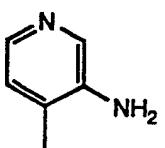
CH₃

OH

H

COCH₃

300

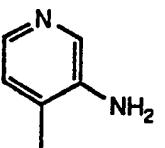
CH₃

OH

CH₃

H

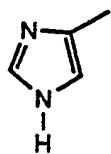
301

CH₃

OH

CH₃COCH₃

302



C=CH

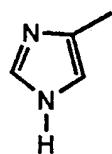
OCH₃

H

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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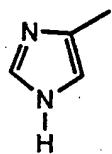
303

 $\text{C}\equiv\text{CH}$ OCH_3

H

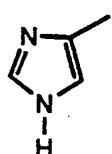
 COCH_3

304

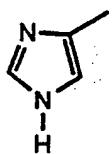
 $\text{C}\equiv\text{CH}$ OCH_3 CH_3

H

305

 $\text{C}\equiv\text{CH}$ OCH_3 CH_3 COCH_3

306

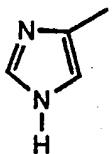
 $\text{C}\equiv\text{CH}$

OH

H

H

307

 $\text{C}\equiv\text{CH}$

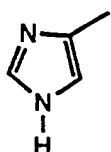
OH

H

 COCH_3

EXAMPLE NO.	A	R ³	R ⁵	E	P
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308



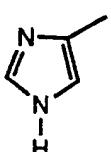
C≡CH

OH

CH₃

H

309

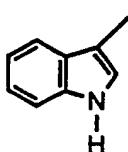


C≡CH

OH

CH₃COCH₃

310



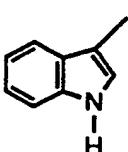
C≡CH

OCH₃

H

H

311



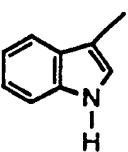
C≡CH

OCH₃

H

COCH₃

312



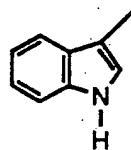
C≡CH

OCH₃CH₃

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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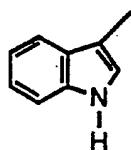
313



C≡CH

OCH₃CH₃COCH₃

314



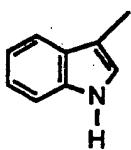
C≡CH

OH

H

H

315



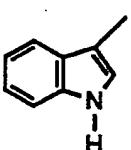
C≡CH

OH

H

COCH₃

316



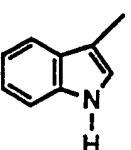
C≡CH

OH

CH₃

H

317



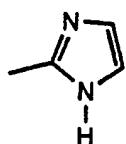
C≡CH

OH

CH₃COCH₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
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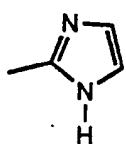
318

 $\text{C}=\text{CH}_2$ OCH_3

H

H

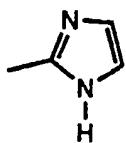
319

 $\text{C}=\text{CH}_2$ OCH_3

H

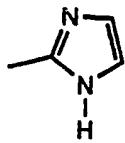
 COCH_3

320

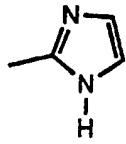
 $\text{C}=\text{CH}_2$ OCH_3 CH_3

H

321

 $\text{C}=\text{CH}_2$ OCH_3 CH_3 COCH_3

322

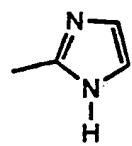
 $\text{C}=\text{CH}_2$ OH

H

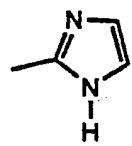
H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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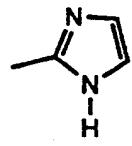
323



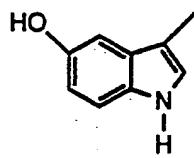
324



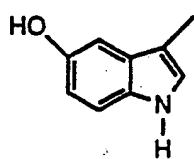
325



326

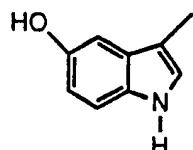


327



EXAMPLE NO.	A	R ³	R ⁵	E	P
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328

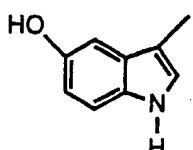


C≡CH

OCH₃CH₃

H

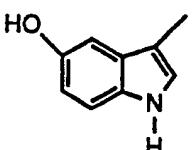
329



C≡CH

OCH₃CH₃COCH₃

330



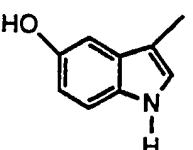
C≡CH

OH

H

H

331



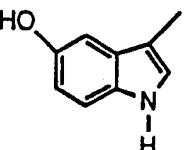
C≡CH

OH

H

COCH₃

332



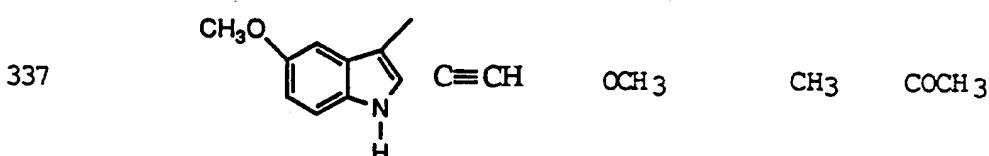
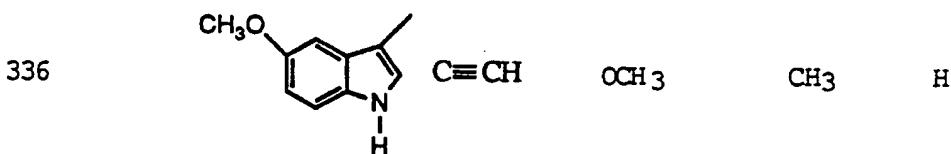
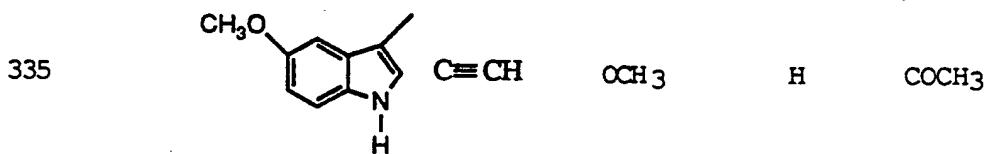
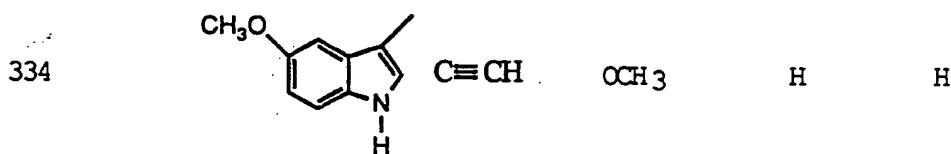
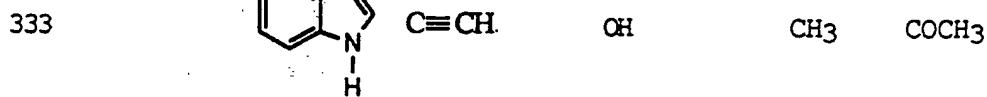
C≡CH

OH

CH₃

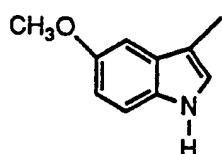
H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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EXAMPLE NO.	A	R ³	R ⁵	E	P
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338



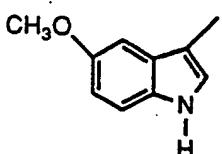
C≡CH

OH

H

H

339



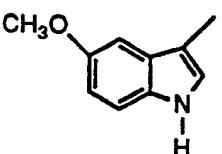
C≡CH

OH

H

COCH₃

340



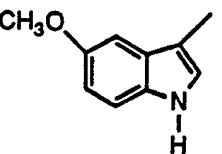
C≡CH

OH

CH₃

H

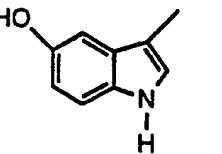
341

CH₃

OH

CH₃COCH₃

342

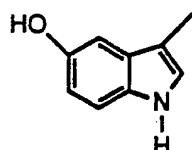
CH₃OCH₃

H

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
----------------	---	----------------	----------------	---	---

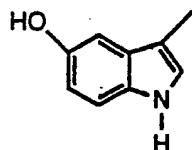
343

CH₃OCH₃

H

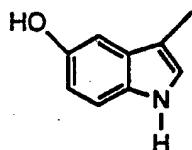
COCH₃

344

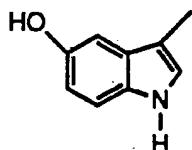
CH₃OCH₃CH₃

H

345

CH₃OCH₃CH₃COCH₃

346

CH₃

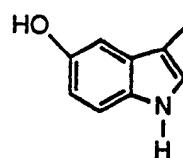
OH

H

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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347

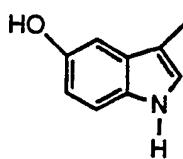
CH₃

OH

H

COCH₃

348

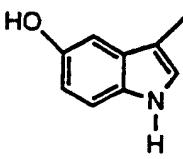
CH₃

OH

CH₃

H

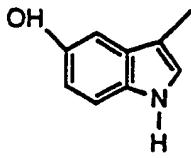
349

CH₃

OH

CH₃COCH₃

350



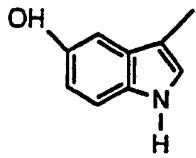
H

OCH₃

H

H

351



H

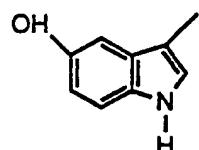
OCH₃

H

COCH₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
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352

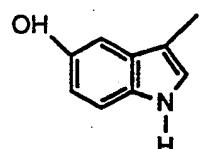


H

OCH₃CH₃

H

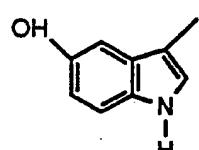
353



H

OCH₃CH₃COCH₃

354



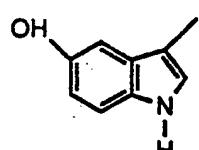
H

OH

H

H

355



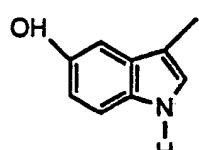
H

OH

H

COCH₃

356



H

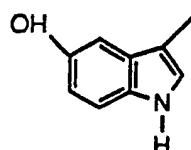
OH

CH₃

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
----------------	---	----------------	----------------	---	---

357

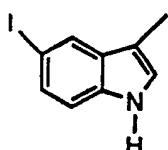


H

OH

CH₃COCH₃

358



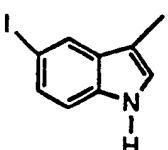
H

OCH₃

H

H

359



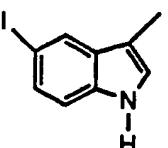
H

OCH₃

H

COCH₃

360

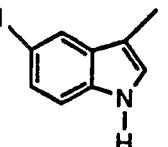


H

OCH₃CH₃

H

361

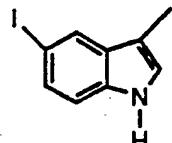


H

OCH₃CH₃COCH₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
----------------	---	----------------	----------------	---	---

362



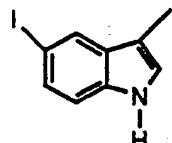
H

OCH₃

H

H

363



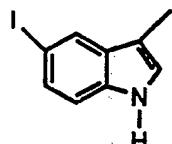
H

OH

H

COCH₃

364



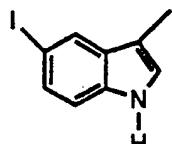
H

OH

H

H

365



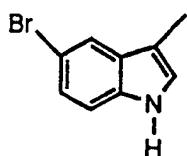
H

OH

CH₃COCH₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
----------------	---	----------------	----------------	---	---

366



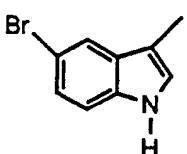
H

OCH₃

H

H

367



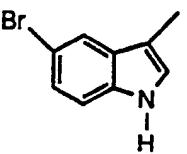
H

OCH₃

H

COCH₃

368

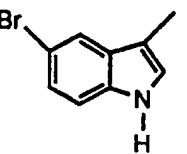


H

OCH₃CH₃

H

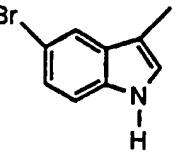
369



H

OCH₃CH₃COCH₃

370



H

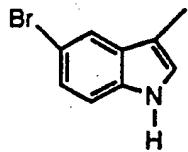
OH

H

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
----------------	---	----------------	----------------	---	---

371



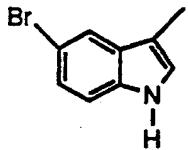
H

OH

H

COCH₃

372



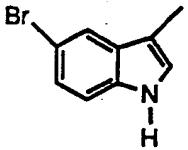
H

OH

CH₃

H

373

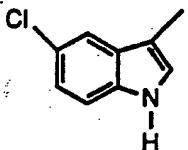


H

OH

CH₃COCH₃

374



H

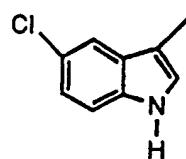
OCH₃

H

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
----------------	---	----------------	----------------	---	---

375



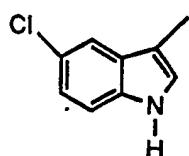
H

OCH₃

H

COCH₃

376

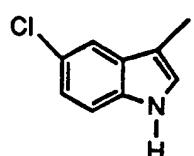


H

OCH₃CH₃

H

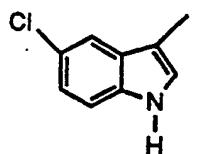
377



H

OCH₃CH₃COCH₃

378



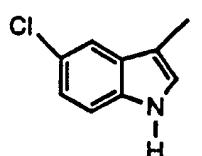
H

OH

H

H

379



H

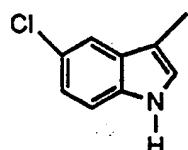
OH

H

COCH₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
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380



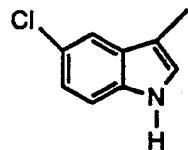
H

OH

CH₃

H

381

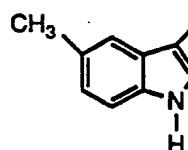


H

OH

CH₃COCH₃

382



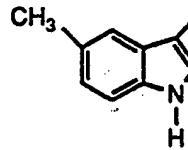
H

OCH₃

H

H

383



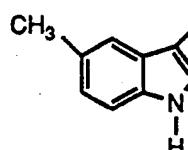
H

OCH₃

H

COCH₃

384



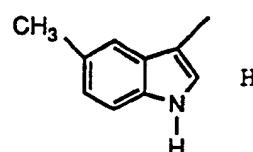
H

OCH₃CH₃

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
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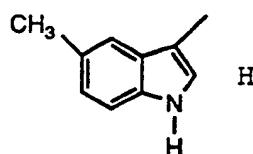
385



H

OCH₃CH₃COCH₃

386



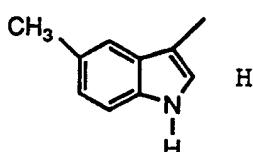
H

OH

H

H

387



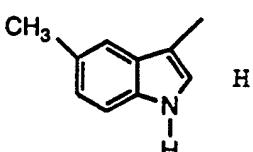
H

OH

H

COCH₃

388



H

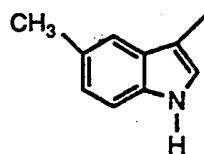
OH

CH₃

H

EXAMPLE NO.	A	R ³	R ⁵	E	P
----------------	---	----------------	----------------	---	---

389

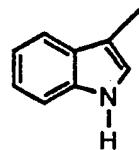


H

OH

CH₃COCH₃

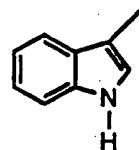
390

CH₃OCH₃

H

H

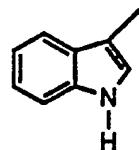
391

CH₃OCH₃

H

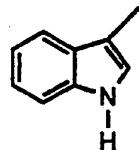
COCH₃

392

CH₃OCH₃CH₃

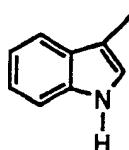
H

393

CH₃OCH₃CH₃COCH₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
----------------	---	----------------	----------------	---	---

394

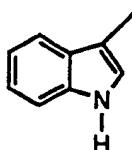
CH₃

OH

H

H

395

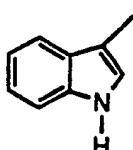
CH₃

OH

H

COCH₃

396

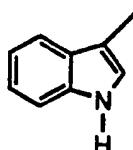
CH₃

OH

H

COCH₃

397

CH₃

OH

CH₃COCH₃

398

C₂HCH=CH₂CH₃

H

H

399

C₂H₅CH=CH₂OCH₃

H

COCH₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
400	C ₂ H ₅	CH=CH ₂	OCH ₃	CH ₃	H
401	C ₂ H ₅	CH=CH ₂	OCH ₃	CH ₃	COCH ₃
402	C ₂ H ₅	CH=CH ₂	OH	H	H
403	C ₂ H ₅	CH=CH ₂	OH	H	COCH ₃
404	C ₂ H ₅	CH=CH ₂	OH	H	COCH ₃
405	C ₂ H ₅	CH=CH ₂	OH	CH ₃	COCH ₃
406	C ₂ H ₅	C≡CH	OCH ₃	H	H
407	C ₂ H ₅	C≡CH	OCH ₃	H	COCH ₃
408	C ₂ H ₅	C≡CH	OCH ₃	CH ₃	H
409	C ₂ H ₅	C≡CH	OCH ₃	CH ₃	COCH ₃

EXAMPLE NO.	A	R ³	R ⁵	E	P
----------------	---	----------------	----------------	---	---

412 C₂H₅ C≡CH OH H COCH₃

5

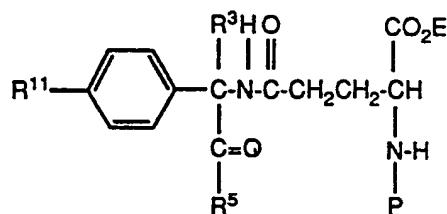
413 C₂H₅ C≡CH OH CH₃ COCH₃

10

15

The following Examples #414-#461 of Table VI are highly preferred conjugates formed from tyrosine hydroxylase inhibitor compounds and glutamic acid derivatives. These tyrosine hydroxylase inhibitors utilized to make these conjugates are embraced by generic Formula III, above.

20

TABLE VI

EXAMPLE NO.	R ¹¹	R ³	R ⁵	E	P
414	OH	H	OH	H	H
415	OH	H	OH	H	COCH ₃
416	OH	H	OH	CH ₃	H
417	OH	H	OH	CH ₃	COCH ₃
418	OH	H	OCH ₃	H	H
419	OH	H	OCH ₃	H	COCH ₃
420	OH	H	OCH ₃	CH ₃	H
421	OH	H	OCH ₃	CH ₃	COCH ₃
422	OH	CH ₃	OH	H	H
423	OH	CH ₃	OH	H	COCH ₃
424	OH	CH ₃	OH	CH ₃	H

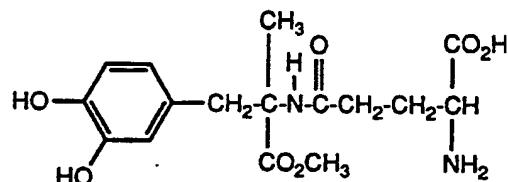
EXAMPLE NO.	R ¹¹	R ³	R ⁵	E	P
425	OH	CH ₃	OH	CH ₃	COCH ₃
426	OH	CH ₃	OCH ₃	H	H
427	OH	CH ₃	OCH ₃	H	COCH ₃
428	OH	CH ₃	OCH ₃	CH ₃	H
429	OH	CH ₃	OCH ₃	CH ₃	COCH ₃
430	OH	H	NH ₂	H	H
431	OH	H	NH ₂	H	COCH ₃
432	OH	H	NH ₂	CH ₃	H
433	OH	H	NH ₂	CH ₃	COCH ₃
434	OH	CH ₃	NH ₂	H	H
435	OH	CH ₃	NH ₂	H	COCH ₃
436	OH	CH ₃	NH ₂	CH ₃	H
437	OH	CH ₃	NH ₂	CH ₃	COCH ₃
438	OCH ₃	H	OH	H	H
439	OCH ₃	H	OH	H	COCH ₃
440	OCH ₃	H	OH	CH ₃	H
441	OCH ₃	H	OH	CH ₃	COCH ₃

EXAMPLE NO.	R ¹¹	R ³	R ⁵	E	P
442	OCH ₃	H	OCH ₃	H	H
443	OCH ₃	H	OCH ₃	H	COCH ₃
444	OCH ₃	H	OCH ₃	CH ₃	H
445	OCH ₃	H	OCH ₃	CH ₃	COCH ₃
446	OCH ₃	CH ₃	OH	H	H
447	OCH ₃	CH ₃	OH	H	COCH ₃
448	OCH ₃	CH ₃	OH	CH ₃	H
449	OCH ₃	CH ₃	OH	CH ₃	COCH ₃
450	OCH ₃	CH ₃	OCH ₃	H	H
451	OCH ₃	CH ₃	OCH ₃	H	COCH ₃
452	OCH ₃	CH ₃	OCH ₃	CH ₃	H
453	OCH ₃	CH ₃	OCH ₃	CH ₃	COCH ₃
454	OCH ₃	H	NH ₂	H	H
455	OCH ₃	H	NH ₂	H	COCH ₃
456	OCH ₃	H	NH ₂	CH ₃	H
457	OCH ₃	H	NH ₂	CH ₃	COCH ₃

EXAMPLE NO.	R ¹¹	R ³	R ⁵	E	P
458	OCH ₃	CH ₃	NH ₂	H	H
459	OCH ₃	CH ₃	NH ₂	H	COCH ₃
460	OCH ₃	CH ₃	NH ₂	CH ₃	H
461	OCH ₃	CH ₃	NH ₂	CH ₃	COCH ₃

The following Examples #462-#857 comprise five classes of highly preferred conjugates composed of dopa-decarboxylase inhibitor compounds and glutamic acid derivatives. Examples #462-#464 are descriptions of specific preparations of such 5 conjugates. Examples #465-#857, as shown in Tables VII-XI, may be prepared by procedures shown in these specific examples and in the foregoing general synthetic procedures of Schemes 1-7.

10

Example 462

15

4-amino-4-carboxy-4-oxobutyl-3-hydroxy- α -methyl-L-tyrosine, methyl ester.

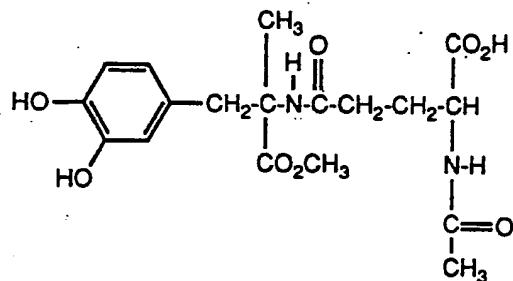
Step. 1: Preparation of α -methyl-L-DOPA, methyl ester, hydrochloride.

A suspension of 29.7 g (141 mmol) of α -methyl-L-DOPA in 300 mL of absolute methanol was cooled to -15°C and treated with 125.8 g (1.06 mol) thionyl chloride under a nitrogen atmosphere. The reaction was allowed to warm to ambient temperature and stir at reflux for 3 days. Concentration followed by trituration with ether gave 31.7g (97%) as an off-white solid: NMR (DMSO-d₆) δ 1.47 (s, 3H), 2.92 (d, J = 12 Hz, 1H), 2.98 (d, J = 12 Hz, 1H), 3.74 (s, 3H), 6.41 (d of d, J = 9 Hz AND 2 Hz, 1H), 6.54 (d, J = 2 Hz, 1H), 6.68 (d, J = 9 Hz, 1H), 8.46-8.90 (br s, 3H), 8.93 (s, 1H), 8.96 (s, 1H).

Step 2: Preparation of 4-amino-4-carboxy-4-oxobutyl-3-hydroxy-
 α -methyl-L-tyrosine, methyl ester.

Under nitrogen, a solution of 32.7 g (108 mmol) of N-

5 Boc-L- γ -glutamic acid- α -t-butyl ester (BACHEM) in 150 mL of
methylene chloride was treated with 11.14 g (54 mmol) of solid
dicyclohexylcarbodiimide (DCC). The reaction was allowed to stir
for 2 hr prior to filtration under a nitrogen atmosphere. The
methylene chloride was removed in vacuo and the residue dissolved
10 in 110 mL of dimethylformamide (DMF). The anhydride solution was
slowly added to a solution of 12.9 g (49 mmol) of the α -methyl-
DOPA ester from step 1 and 12.6 g (98 mmol) of
diisopropylethylamine (DIEA) in 50 mL of anhydrous DMF. The
reaction was allowed to stir overnight and was concentrated in
15 vacuo. The residue was dissolved in ethyl acetate, washed with
1N citric acid, 1N NaHCO₃, water, and brine, dried (Na₂SO₄), and
concentrated in vacuo to give the protected coupled product; a
solution of this material in 100 mL of methylene chloride was
cooled to 0°C and treated with 400 mL of trifluoroacetic acid
20 (TFA) under nitrogen. The reaction was allowed to warm to
ambient temperature and stir for 72 hr. Concentration in vacuo
gave 4-amino-4-carboxy-4-oxobutyl-3-hydroxy- α -methyl-L-tyrosine,
methyl ester: NMR (DMSO-d₆) δ 1.40 (s, 3H), 1.85-2.30 (m, 2H),
2.30-2.50 (m, 2H), 2.77 (d, J = 12 Hz, 1H), 3.00 (d, J = 12 Hz,
25 1H), 3.58 (s, 3H), 3.85-4.10 (m, 1H), 6.29 (d of d, J = 9 Hz and
2 Hz, 1H), 6.45 (d, J = 2 Hz, 1H), 6.62 (d, J = 9 Hz, 1H); MS
(FAB) m/e (rel intensity) 355 (92), 225 (51), 148 (35).

Example 463

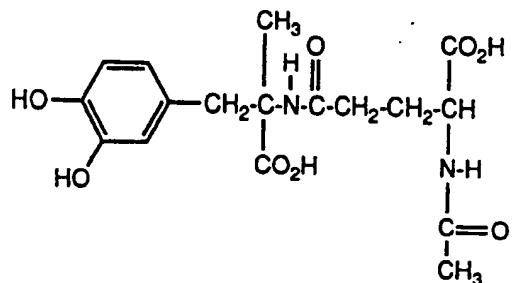
- 5 N-[4-(acetylamino)-4-carboxy-4-oxobutyl]-3-hydroxy- α -methyl-L-tyrosine, methyl ester.

The compound of Example 462 was dissolved in 100 mL of degassed water and under nitrogen the pH adjusted to 9 with 1 M K₂CO₃. The solution was cooled to 0°C and 12 mL (127 mmol) of acetic anhydride and 180 mL (180 mmol) of 1 M K₂CO₃ was added every 30 min. for 5h; the pH was maintained at 9 and the reaction temperature kept below 5°C. After the last addition, the reaction was allowed to warm to ambient temperature overnight.

10 The pH was adjusted to 3 with 3M HCl and concentrated to 100 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) using a 5-15% gradient of acetonitrile/water (0.05% TFA) gave 14.0g (49%) of colorless product: NMR (DMSO-d₆) δ 1.15 (s, 3H), 1.70-1.83 (m, 2H), 1.85 (s, 3H), 1.87-2.00 (m, 2H), 2.15 (t, J = 7 Hz, 2H), 2.75 (d, J = 12 Hz, 1H), 3.00 (d, J = 12 Hz, 1H), 3.55 (s, 3H), 4.10-4.22 (m, 1H), 6.29 (d of d, J = 9 Hz and 2Hz, 1H), 6.43 (d, J = 2Hz, 1H), 6.60 (d, J = 9 Hz, 1H), 7.96 (s, 1H), 8.12 (d, J = 8 Hz, 1H); MS (FAB) m/e (rel intensity) 397 (100), 365 (10), 226 (70), 166 (90), 153 (22), 130 (72), 102 (28).

15

20

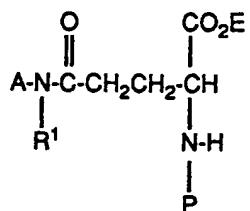
Example 464

- 5 N-[4-(acetylamino)-4-carboxy-4-oxobutyl]-3-hydroxy- α -methyl-L-tyrosine.

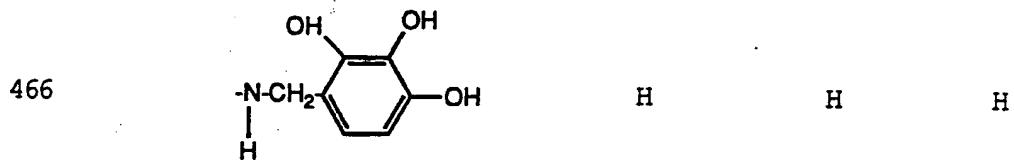
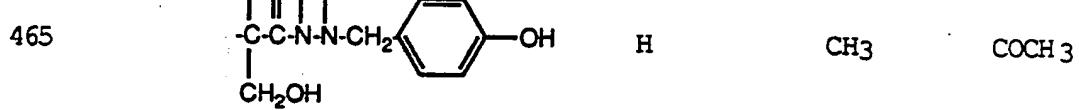
A solution of 13.5 g (102 mmol) of the compound of Example 463 in 34 mL of water was cooled to 0°C and treated with 102 mL (102 mmol) of 1N NaOH (all solutions were degassed in vacuo and flushed with nitrogen prior to use). The reaction was stirred at ambient temperature for 5 hr and the pH adjusted to pH 1 with 6N HCl. Purification by reverse phase chromatography (Waters Deltaprep-3000) using a 2-10% gradient of acetonitrile/water (0.05% TFA) gave 8.9 g (68%) of colorless product: NMR (DMSO-d₆) δ 1.18 (s, 3H), 1.70-1.83 (m, 2H), 1.85 (s, 3H), 1.87-2.00 (m, 2H), 2.15 (t, J = 7 Hz, 2H), 2.75 (d, J = 12 Hz, 1H), 3.05 (d, J = 12 Hz, 1H), 4.10-4.23 (m, 1H), 6.31 (d of d, J = 9 Hz and 2 Hz, 1H), 6.47 (d, J = 2 Hz, 1H), 6.60 (d, J = 9 Hz, 1H), 7.71 (s, 1H), 8.15 (d, J = 8 Hz, 1H); MS (FAB) m/e (rel intensity) 383 (23), 212 (10), 166 (18), 130 (21), 115 (23); HRMS. Calcd for M + H: 383.1454. Found: 383.1450. Anal: Calcd for C₁₇H₂₂N₂O₈•1.06 H₂O•0.85 TFA: C, 48.67; H, 5.59; N, 6.46; F, 3.73. Found: C, 49.02; H, 5.73; N, 6.40; F, 3.70.

25

The following Examples #465-#541 of Table VII are highly preferred conjugates composed of dopa-decarboxylase inhibitor compounds and glutamic acid derivatives. These dopa-decarboxylase inhibitors utilized to make these conjugates are 30 embraced by generic Formula IV, above.

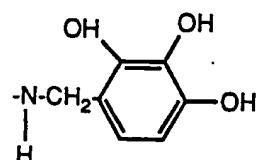
TABLE VII

EXAMPLE NO.	A	R ¹	E	P
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EXAMPLE NO.	A	R ¹	E	P
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468

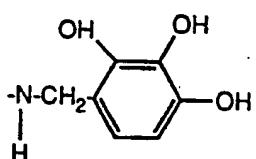


H

CH₃

H

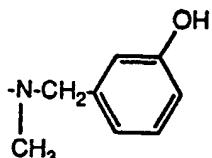
469



H

CH₃COCH₃

470

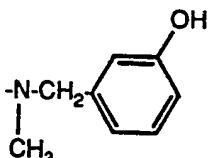


H

H

H

471



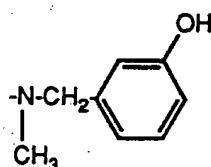
H

H

COCH₃

EXAMPLE NO.	A	R ¹	E	P
----------------	---	----------------	---	---

472

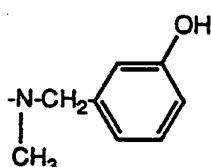


H

CH₃

H

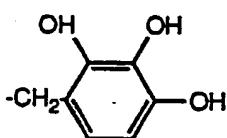
473



H

CH₃COCH₃

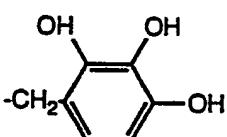
474

NH₂

H

H

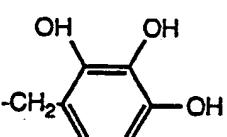
475

NH₂

H

COCH₃

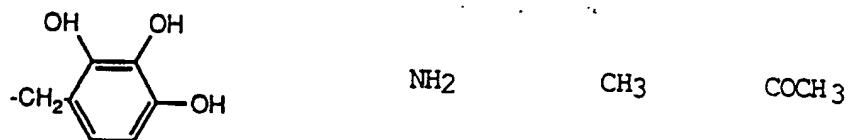
476

NH₂CH₃

H

EXAMPLE NO.	A	R ¹	E	P
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477

NH₂CH₃COCH₃

478

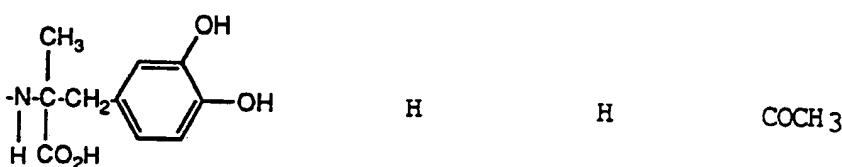


H

H

H

479



H

H

COCH₃

480

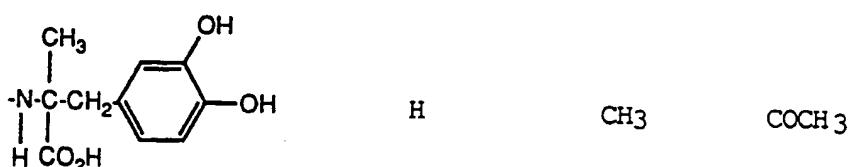


H

CH₃

H

481

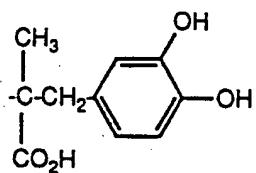


H

CH₃COCH₃

EXAMPLE NO.	A	R ¹	E	P
----------------	---	----------------	---	---

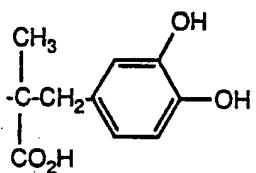
482

NH₂

H

H

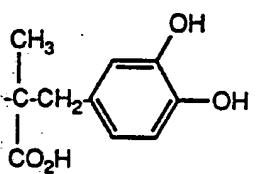
483

NH₂

H

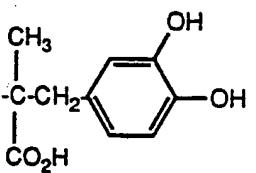
COCH₃

484

NH₂CH₃

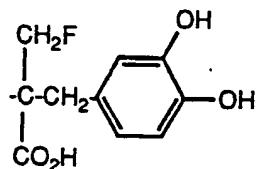
H

485

NH₂CH₃COCH₃

EXAMPLE NO.	A	R ¹	E	P
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486

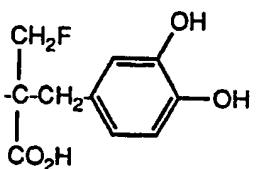


H

H

H

487

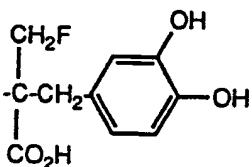


H

H

COCH₃

488

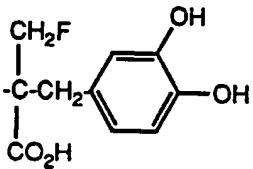


H

CH₃

H

489

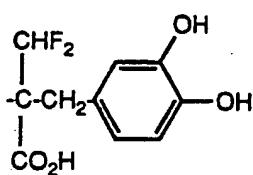


H

CH₃COCH₃

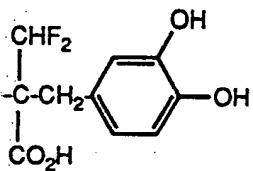
EXAMPLE NO.	A	R ¹	E	P
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490

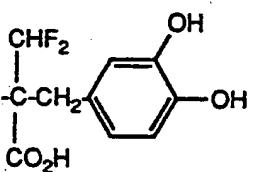


H H H

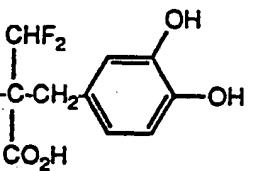
491

H H COCH₃

492

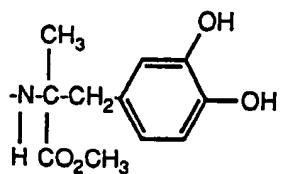
H CH₃ H

493

H CH₃ COCH₃

EXAMPLE NO.	A	R ¹	E	P
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494

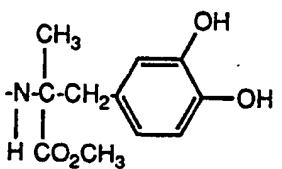


H

H

H

495

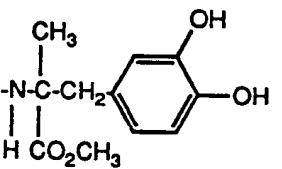


H

H

COCH₃

496

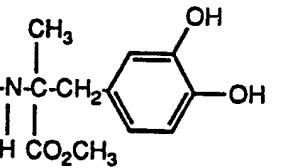


H

CH₃

H

497

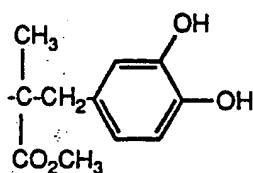


H

CH₃COCH₃

EXAMPLE NO.	A	R ¹	E	P
----------------	---	----------------	---	---

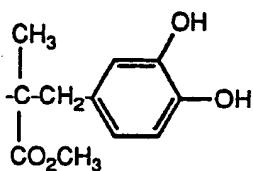
498

NH₂

H

H

499

NH₂

H

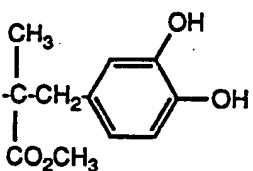
COCH₃

500

NH₂CH₃

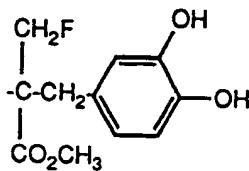
H

501

NH₂CH₃COCH₃

EXAMPLE NO.	A	R ¹	E	P
----------------	---	----------------	---	---

502

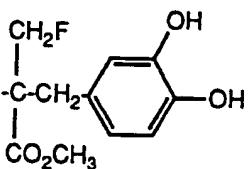


H

H

H

503

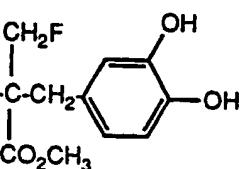


H

H

COCH₃

504

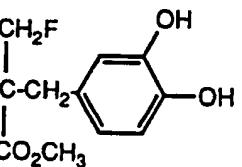


H

CH₃

H

505

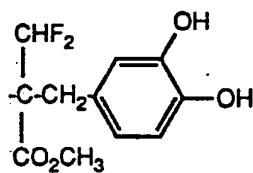


H

CH₃COCH₃

EXAMPLE NO.	A	R ¹	E	P
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506

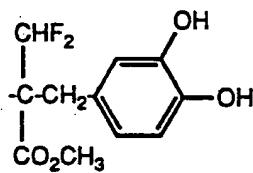


H

H

H

507

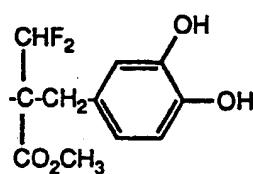


H

H

COCH₃

508

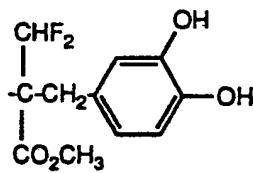


H

CH₃

H

509

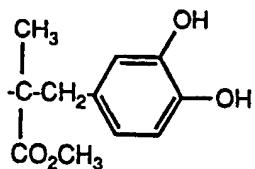


H

CH₃COCH₃

EXAMPLE NO.	A	R ¹	E	P
----------------	---	----------------	---	---

510

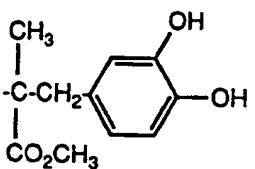


H

H

H

511

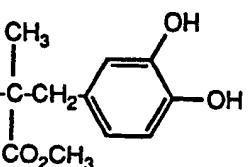


H

H

COCH₃

512



H

CH₃

H

513

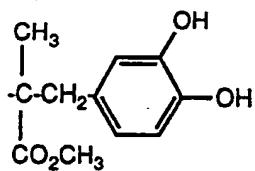


H

CH₃COCH₃

EXAMPLE NO.	A	R ¹	E	P
----------------	---	----------------	---	---

514

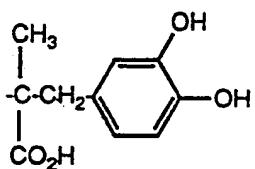


H

H

H

515

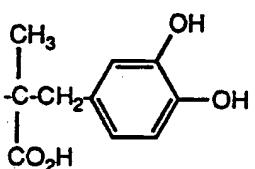


H

H

COCH₃

516

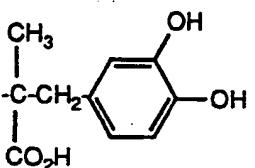


H

CH₃

H

517

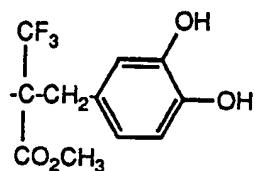


H

CH₃COCH₃

EXAMPLE **A** **R¹** **E** **P**

518

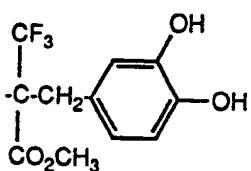


H

1

H

519

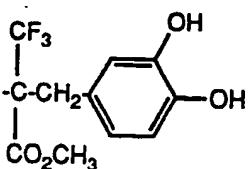


H

H

COCH 3

520

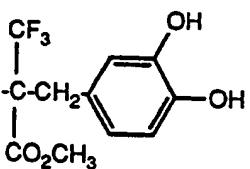


H

CH₃

H

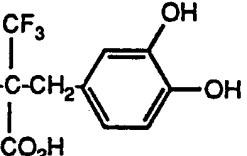
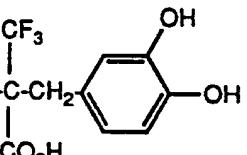
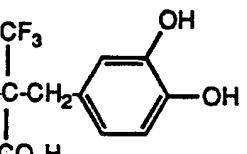
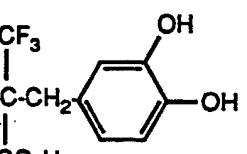
521



H

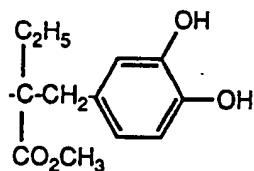
CH_3

COCH 3

EXAMPLE NO.	A	R ¹	E	P
522		H	H	H
523		H	H	COCH ₃
524		H	CH ₃	H
525		H	CH ₃	COCH ₃

EXAMPLE NO.	A	R ¹	E	P
----------------	---	----------------	---	---

526



H

H

H

527

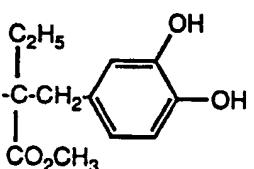


H

H

COCH₃

528

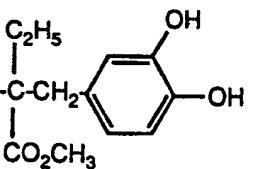


H

CH₃

H

529

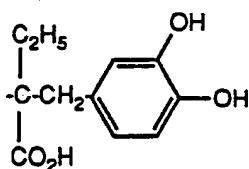


H

CH₃COCH₃

EXAMPLE NO.	A	R ¹	E	P
----------------	---	----------------	---	---

530

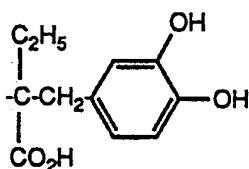


H

H

H

531

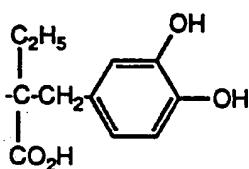


H

H

COCH₃

532

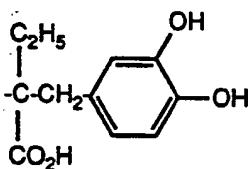


H

CH₃

H

533

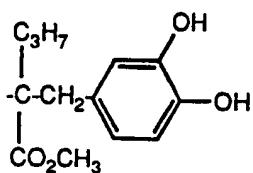


H

CH₃COCH₃

EXAMPLE NO.	A	R ¹	E	P
----------------	---	----------------	---	---

534

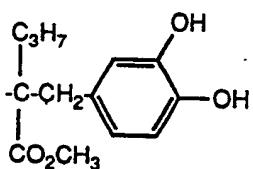


H

H

H

535

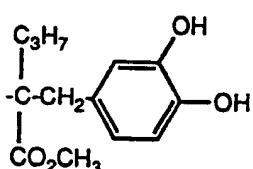


H

H

COCH₃

536

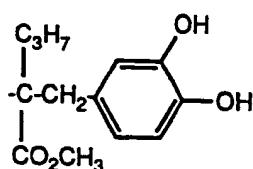


H

CH₃

H

537

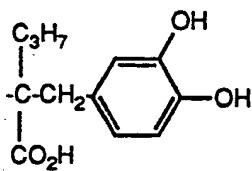


H

CH₃COCH₃

EXAMPLE NO.	A	R ¹	E	P
----------------	---	----------------	---	---

538

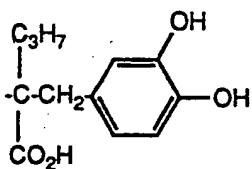


H

H

H

539

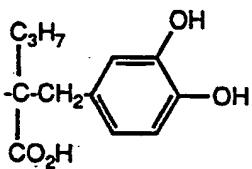


H

H

COCH₃

540

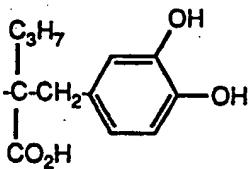


H

CH₃

H

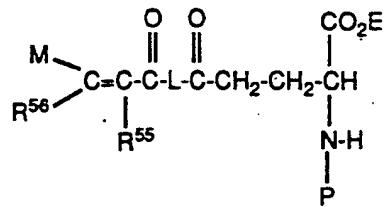
541



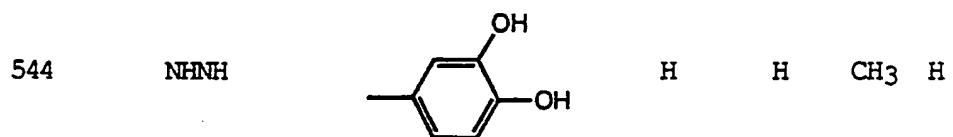
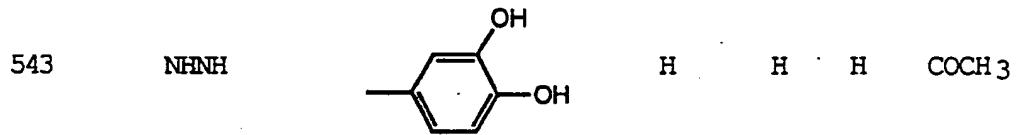
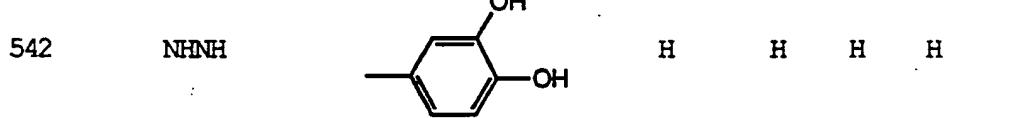
H

CH₃COCH₃

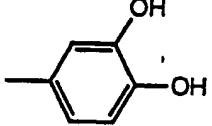
The following Examples #542-#577 of Table VIII are highly preferred conjugates composed of dopa-decarboxylase inhibitor compounds and glutamic acid derivatives. These dopa-decarboxylase inhibitors utilized to make these conjugates are embraced by generic Formula VIII, above.

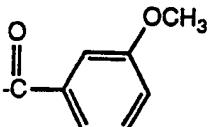
TABLE VIII

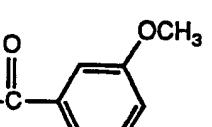
EXAMPLE NO.	L	M	R ⁵⁶	R ⁵⁵	E	P
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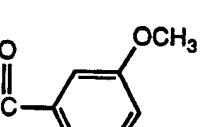


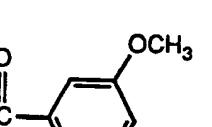
EXAMPLE NO.	L	M	R56	R55	E	P
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545 NHHH  H H CH₃ COCH₃

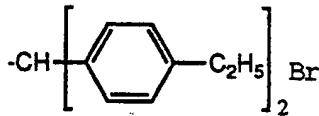
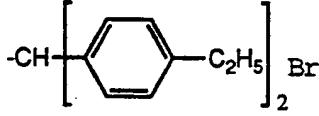
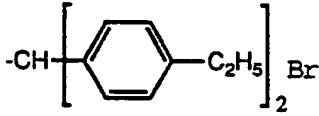
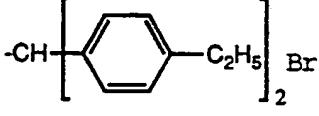
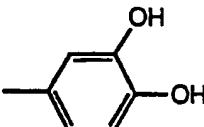
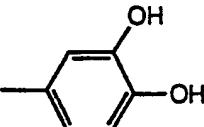
546 NHHH  Br H H H

547 NHHH  Br H H COCH₃

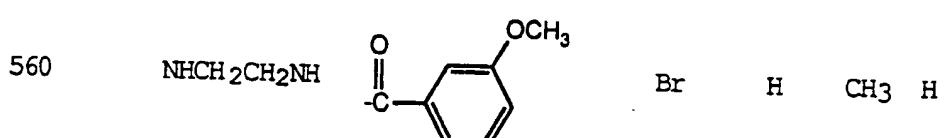
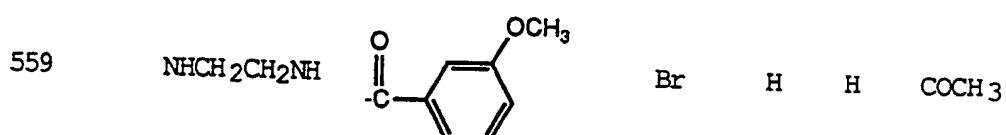
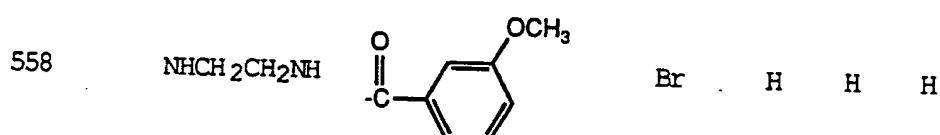
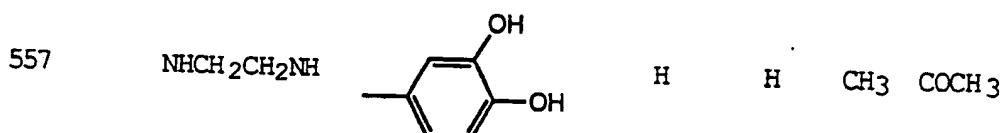
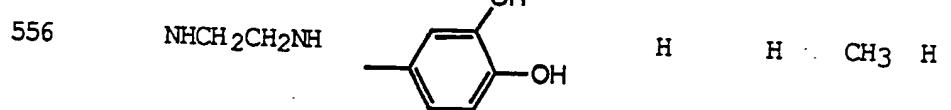
548 NHHH  Br H CH₃ H

549 NHHH  Br H CH₃ COCH₃

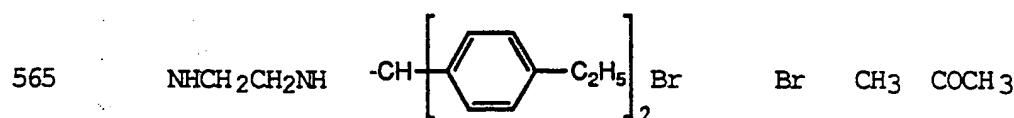
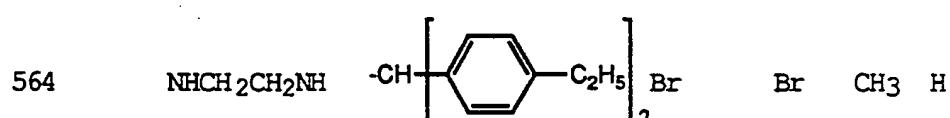
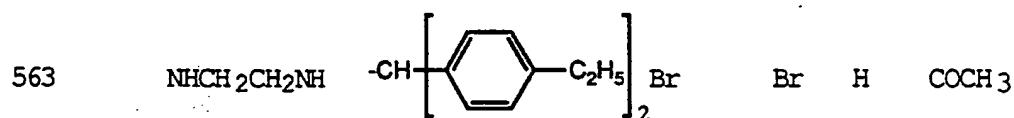
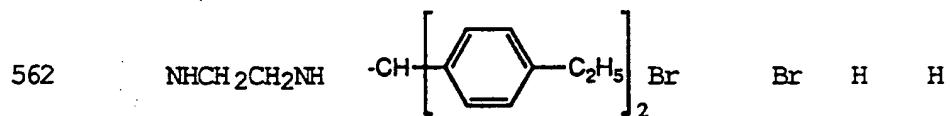
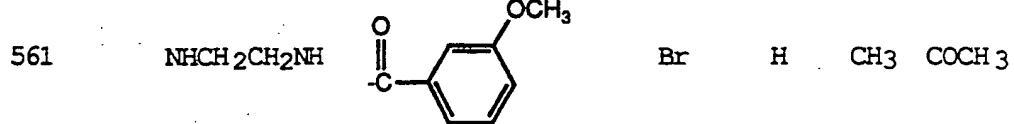
EXAMPLE NO.	L	M	R ⁵⁶	R ⁵⁵	E	P
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- 550 NHHN -CH-[]₂Br Br H H
- 551 NHHN -CH-[]₂Br Br H COCH₃
- 552 NHHN -CH-[]₂Br Br CH₃ H
- 553 NHHN -CH-[]₂Br Br CH₃ COCH₃
- 554 NHCH₂CH₂NH - H H H H
- 555 NHCH₂CH₂NH - H H H COCH₃

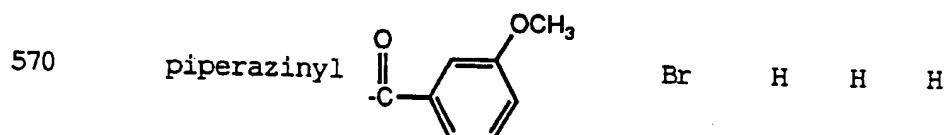
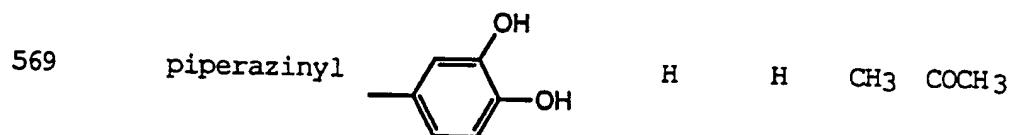
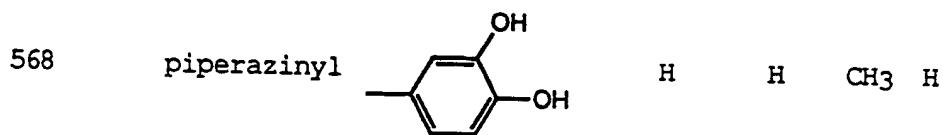
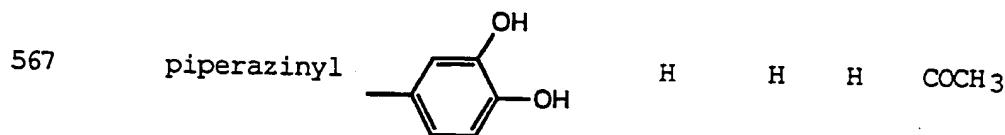
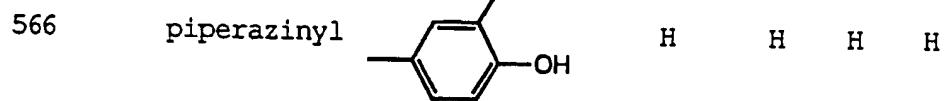
EXAMPLE NO.	L	M	R56	R55	E	P
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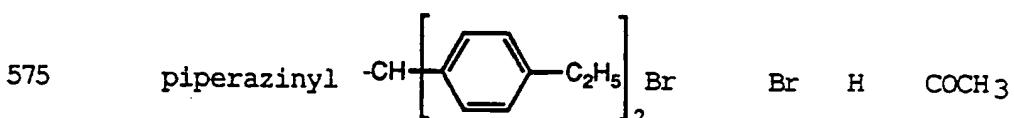
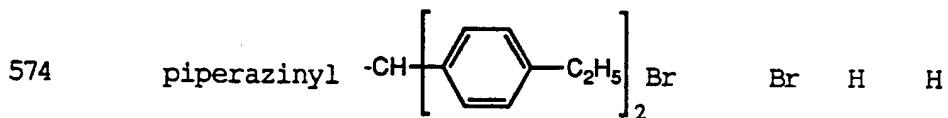
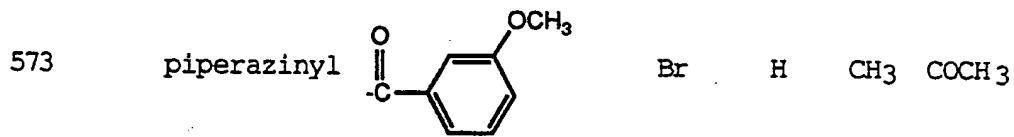
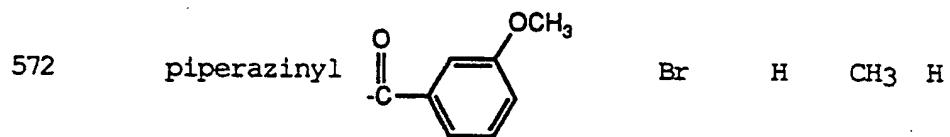
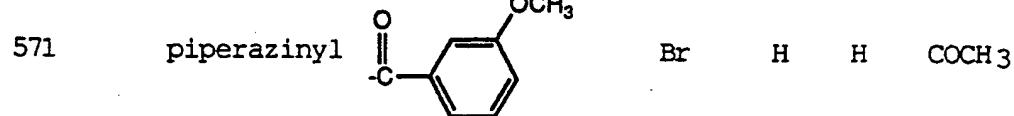
EXAMPLE NO.	L	M	R ⁵⁶	R ⁵⁵	E	P
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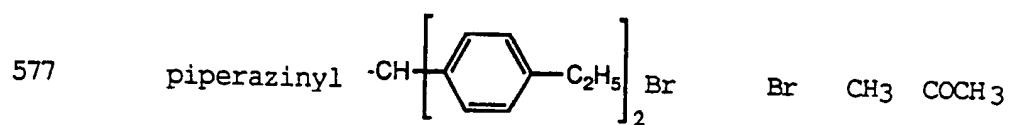
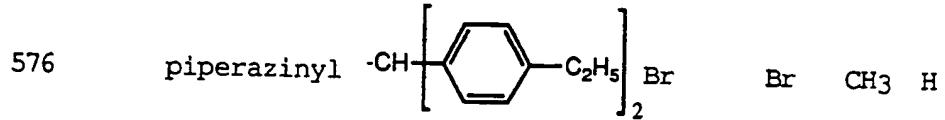
EXAMPLE NO.	L	M	R ⁵⁶	R ⁵⁵	E	P
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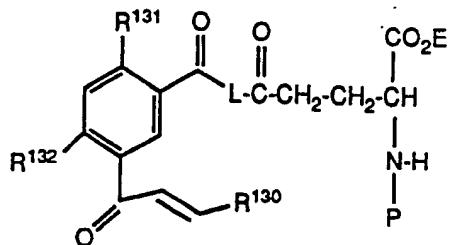
EXAMPLE NO.	L	M	R56	R55	E	P
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EXAMPLE NO.	L	M	R56	R55	E	P
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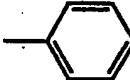


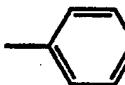
The following Examples #578-#757 of Table IX are highly preferred conjugates composed of dopa-decarboxylase inhibitor compounds and glutamic acid derivatives. These dopa-decarboxylase inhibitors utilized to make these conjugates are 5 benzoic acid type derivatives based on the list of similar compounds described earlier.

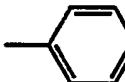
TABLE IX

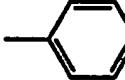
EXAMPLE NO.	L	R ¹³⁰	R ¹³¹	R ¹³²	E	P
578	NHNH	H	OH	OH	H	H
579	NHNH	H	OH	OH	H	COCH ₃
580	NHNH	H	OH	OH	CH ₃	H
581	NHNH	H	OH	OH	CH ₃	COCH ₃
582	NHNH		OH	OH	H	H
583	NHNH		OH	OH	H	COCH ₃
584	NHNH		OH	OH	CH ₃	H

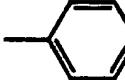
EXAMPLE NO.	L	R ¹³⁰	R ¹³¹	R ¹³²	E	P
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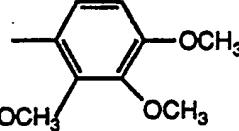
585 NHHH  OH OH CH₃ COCH₃

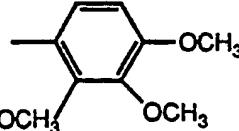
586 NHHH  OH OH H H

587 NHHH  OH OH H COCH₃

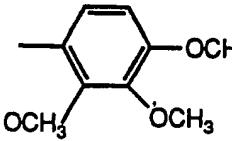
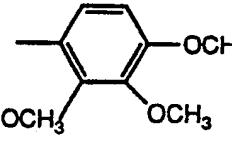
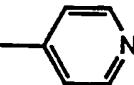
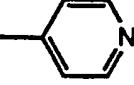
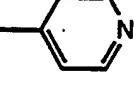
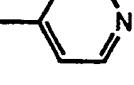
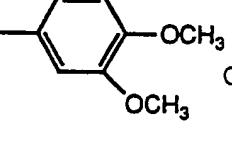
588 NHHH  OH OH CH₃ H

589 NHHH  OH OH CH₃ COCH₃

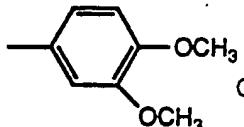
590 NHHH  OCH₃ OCH₃ OCH₃ H H

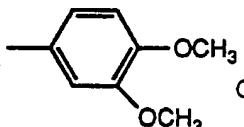
591 NHHH  OCH₃ OCH₃ OCH₃ H COCH₃

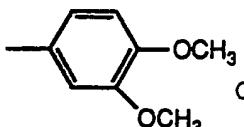
EXAMPLE NO.	L	R ¹³⁰	R ¹³¹	R ¹³²	E	P
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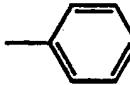
- 592 NHHN  OCH₃ OCH₃ CH₃ H
- 593 NHHN  OCH₃ OCH₃ CH₃ COCH₃
- 594 NHHN  OCH₃ OCH₃ H H
- 595 NHHN  OCH₃ OCH₃ H COCH₃
- 596 NHHN  OCH₃ OCH₃ CH₃ H
- 597 NHHN  OCH₃ OCH₃ CH₃ COCH₃
- 598 NHHN  OCH₃ OCH₃ H H

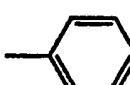
EXAMPLE NO.	L	R ¹³⁰	R ¹³¹	R ¹³²	E	P
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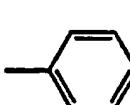
599 NHHH  OCH₃ OCH₃ OCH₃ H COCH₃

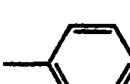
600 NHHH  OCH₃ OCH₃ OCH₃ CH₃ H

601 NHHH  OCH₃ OCH₃ OCH₃ CH₃ COCH₃

602 NHHH  OCH₃ OCH₃ H H

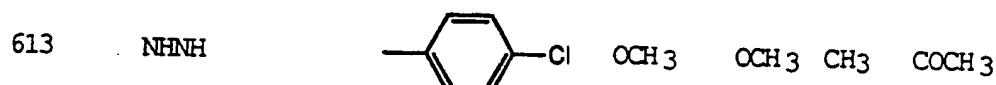
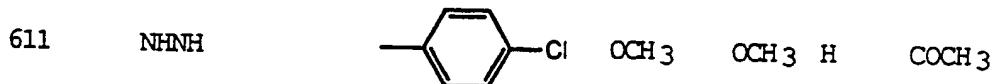
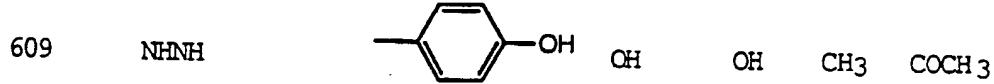
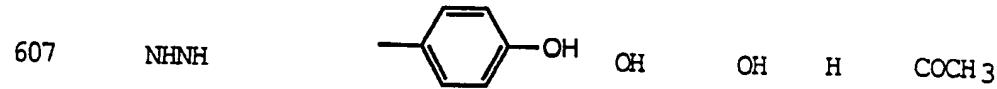
603 NHHH  OCH₃ OCH₃ H COCH₃

604 NHHH  OCH₃ OCH₃ CH₃ H

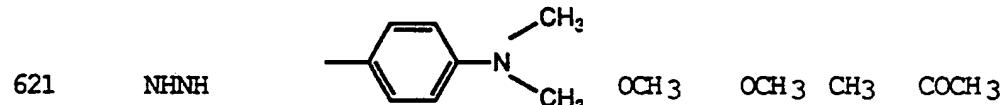
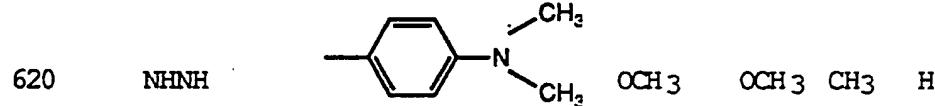
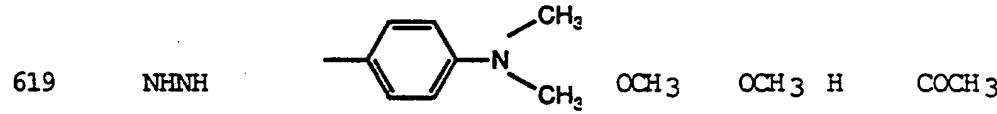
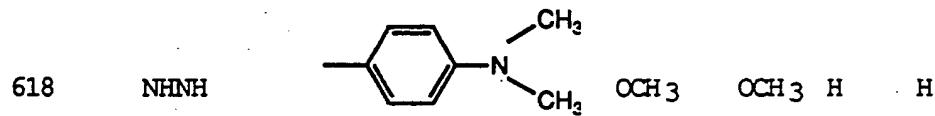
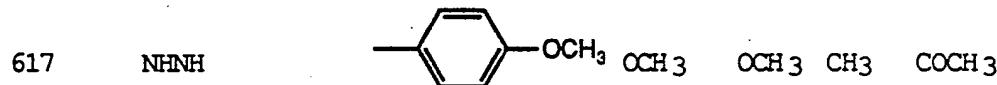
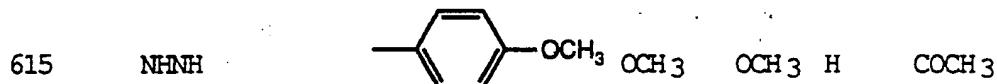
605 NHHH  OCH₃ OCH₃ CH₃ COCH₃

606 NHHH  OH OH H H

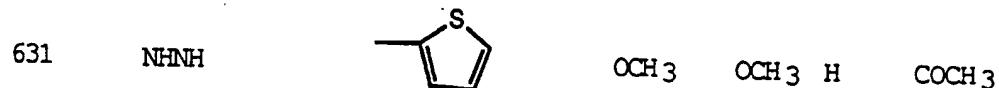
EXAMPLE NO.	L	R ¹³⁰	R ¹³¹	R ¹³²	E	P
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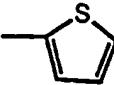
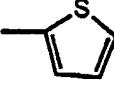
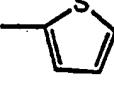
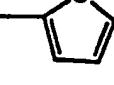
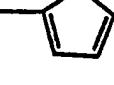
EXAMPLE NO.	L	R ¹³⁰	R ¹³¹	R ¹³²	E	P
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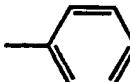
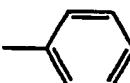
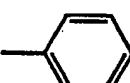
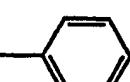
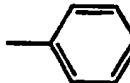
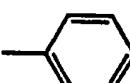
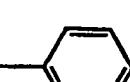
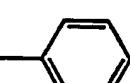
EXAMPLE NO.	L	R ¹³⁰	R ¹³¹	R ¹³²	E	P
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EXAMPLE NO.	L	R ¹³⁰	R ¹³¹	R ¹³²	E	P
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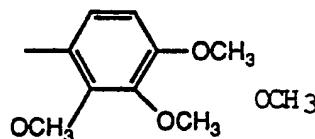
632	NHNH		OCH ₃	OCH ₃	CH ₃	H
633	NHNH		OCH ₃	OCH ₃	CH ₃	COCH ₃
634	NHNH		OH	OH	H	H
635	NHNH		OH	OH	H	COCH ₃
636	NHNH		OH	OH	CH ₃	H
637	NHNH		OH	OH	CH ₃	COCH ₃
638	NHCH ₂ CH ₂ NH	H	OH	OH	H	H
639	NHCH ₂ CH ₂ NH	H	OH	OH	H	COCH ₃
640	NHCH ₂ CH ₂ NH	H	OH	OH	CH ₃	H
641	NHCH ₂ CH ₂ NH	H	OH	OH	CH ₃	COCH ₃

EXAMPLE NO.	L	R ¹³⁰	R ¹³¹	R ¹³²	E	P
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642	NHCH ₂ CH ₂ NH		OH	OH	H	H
643	NHCH ₂ CH ₂ NH		OH	OH	H	COCH ₃
644	NHCH ₂ CH ₂ NH		OH	OH	CH ₃	H
645	NHCH ₂ CH ₂ NH		OH	OH	CH ₃	COCH ₃
646	NHCH ₂ CH ₂ NH		OH	OH	H	H
647	NHCH ₂ CH ₂ NH		OH	OH	H	COCH ₃
648	NHCH ₂ CH ₂ NH		OH	OH	CH ₃	H
649	NHCH ₂ CH ₂ NH		OH	OH	CH ₃	COCH ₃

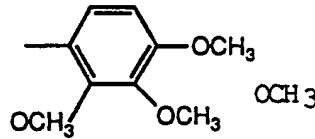
EXAMPLE NO.	L	R ¹³⁰	R ¹³¹	R ¹³²	E	P
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650

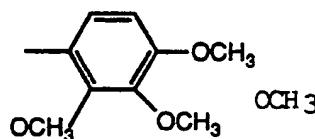
NHCH₂CH₂NHOCH₃OCH₃

H

651

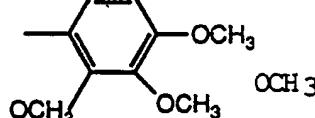
NHCH₂CH₂NHOCH₃OCH₃COCH₃

652

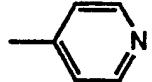
NHCH₂CH₂NHOCH₃OCH₃

H

653

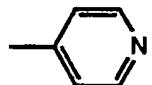
NHCH₂CH₂NHOCH₃OCH₃COCH₃

654

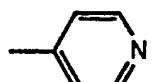
NHCH₂CH₂NHOCH₃OCH₃

H

655

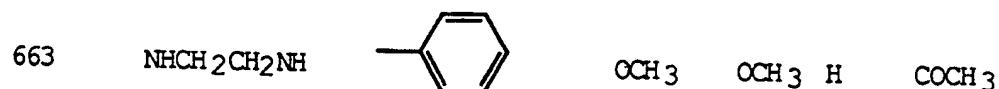
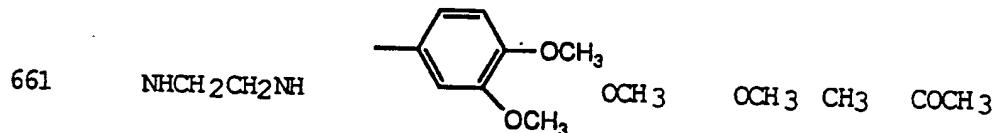
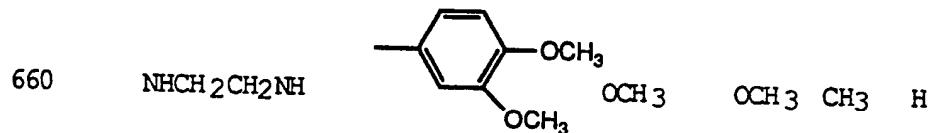
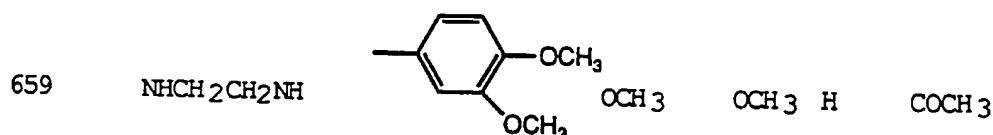
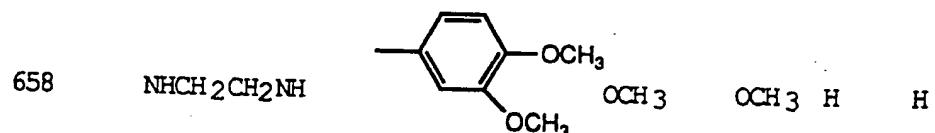
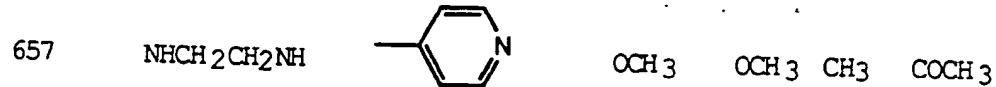
NHCH₂CH₂NHOCH₃OCH₃COCH₃

656

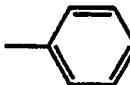
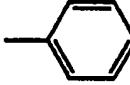
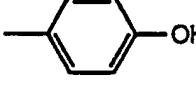
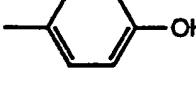
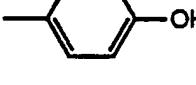
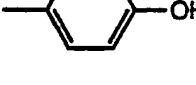
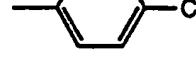
NHCH₂CH₂NHOCH₃OCH₃

H

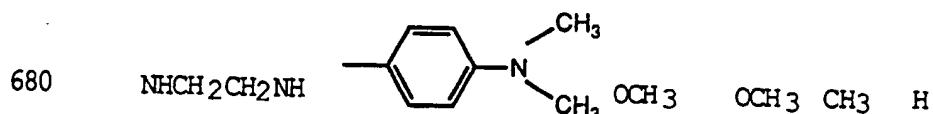
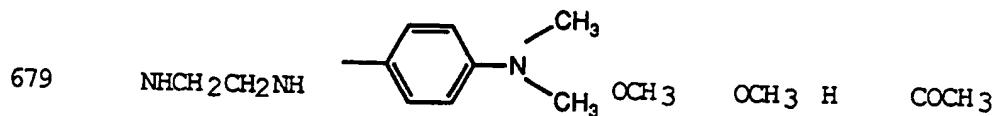
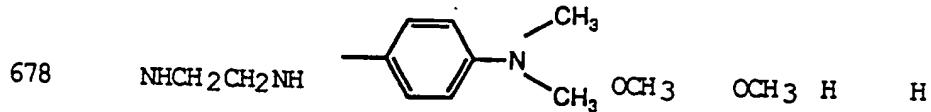
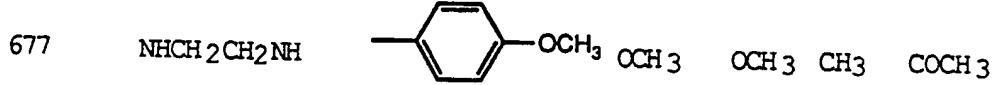
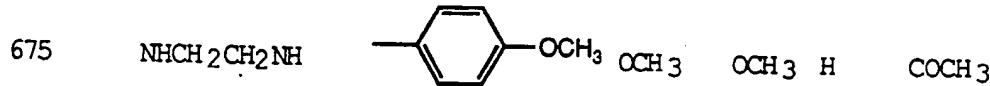
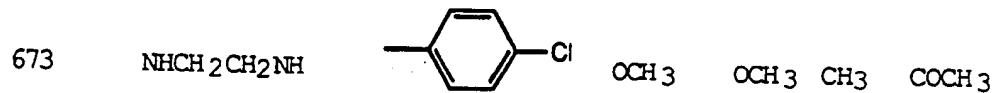
EXAMPLE NO.	L	R130	R131	R132	E	P
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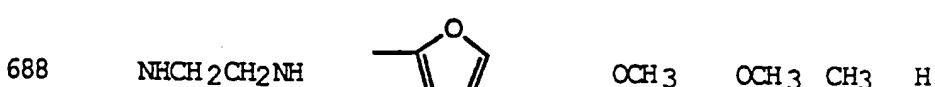
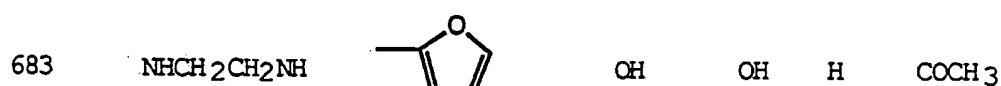
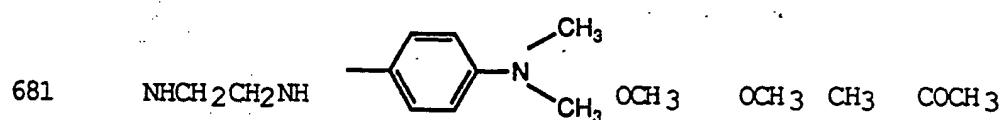
EXAMPLE NO.	L	R ¹³⁰	R ¹³¹	R ¹³²	E	P
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664	NHCH ₂ CH ₂ NH		OCH ₃	OCH ₃	CH ₃	H
665	NHCH ₂ CH ₂ NH		OCH ₃	OCH ₃	CH ₃	COCH ₃
666	NHCH ₂ CH ₂ NH		OH	OH	H	H
667	NHCH ₂ CH ₂ NH		OH	OH	H	COCH ₃
668	NHCH ₂ CH ₂ NH		OH	OH	CH ₃	H
669	NHCH ₂ CH ₂ NH		OH	OH	CH ₃	COCH ₃
670	NHCH ₂ CH ₂ NH		OCH ₃	OCH ₃	H	H
671	NHCH ₂ CH ₂ NH		OCH ₃	OCH ₃	H	COCH ₃
672	NHCH ₂ CH ₂ NH		OCH ₃	OCH ₃	CH ₃	H

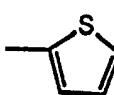
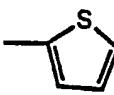
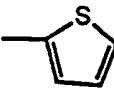
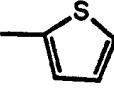
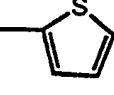
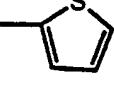
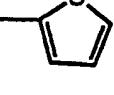
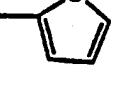
EXAMPLE NO.	L	R130	R131	R132	E	P
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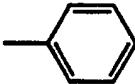
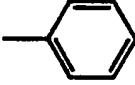
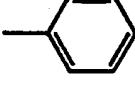
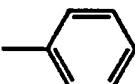
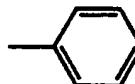
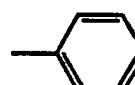


EXAMPLE NO.	L	R130	R131	R132	E	P
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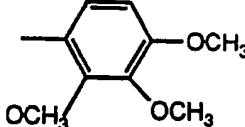
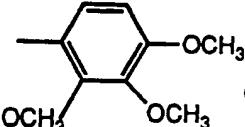
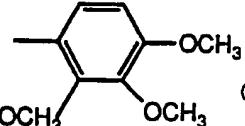
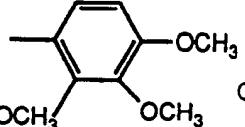
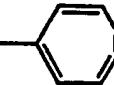


EXAMPLE NO.	L	R130	R131	R132	E	P
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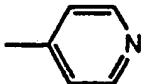
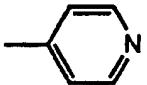
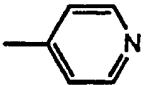
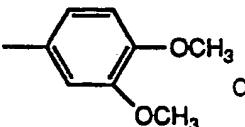
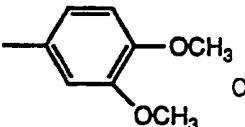
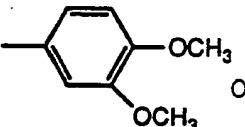
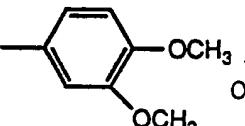
690	NHCH ₂ CH ₂ NH		OCH ₃	OCH ₃	H	H
691	NHCH ₂ CH ₂ NH		OCH ₃	OCH ₃	H	COCH ₃
692	NHCH ₂ CH ₂ NH		OCH ₃	OCH ₃	CH ₃	H
693	NHCH ₂ CH ₂ NH		OCH ₃	OCH ₃	CH ₃	COCH ₃
694	NHCH ₂ CH ₂ NH		OH	OH	H	H
695	NHCH ₂ CH ₂ NH		OH	OH	H	COCH ₃
696	NHCH ₂ CH ₂ NH		OH	OH	CH ₃	H
697	NHCH ₂ CH ₂ NH		OH	OH	CH ₃	COCH ₃
698	piperazinyl	H		OH	OH	H

EXAMPLE NO.	L	R130	R131	R132	E	P
699	piperazinyl	H	OH	OH	H	COCH ₃
700	piperazinyl	H	OH	OH	CH ₃	H
701	piperazinyl	H	OH	OH	CH ₃	COCH ₃
702	piperazinyl		OH	OH	H	H
703	piperazinyl		OH	OH	H	COCH ₃
704	piperazinyl		OH	OH	CH ₃	H
705	piperazinyl		OH	OH	CH ₃	COCH ₃
706	piperazinyl		OH	OH	H	H
707	piperazinyl		OH	OH	H	COCH ₃

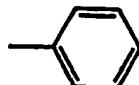
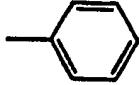
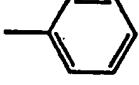
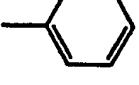
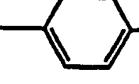
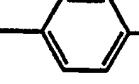
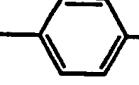
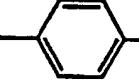
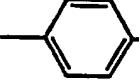
EXAMPLE NO.	L	R130	R131	R132	E	P
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- 708 piperazinyl  OH OH CH₃ H
- 709 piperazinyl  OH OH CH₃ COCH₃
- 710 piperazinyl  OCH₃ OCH₃ OCH₃ H H
- 711 piperazinyl  OCH₃ OCH₃ OCH₃ H COCH₃
- 712 piperazinyl  OCH₃ OCH₃ OCH₃ CH₃ H
- 713 piperazinyl  OCH₃ OCH₃ OCH₃ CH₃ COCH₃
- 714 piperazinyl  OCH₃ OCH₃ H H

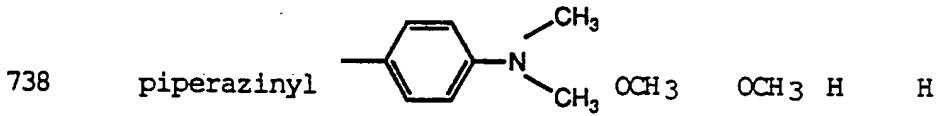
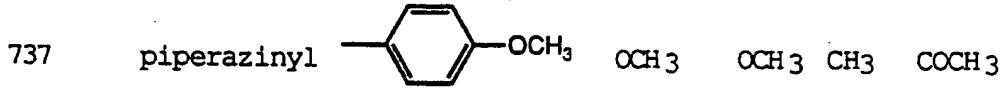
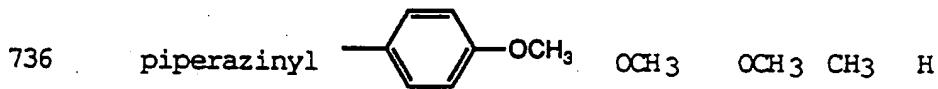
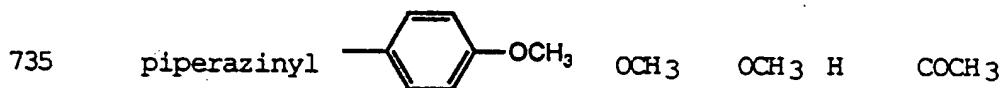
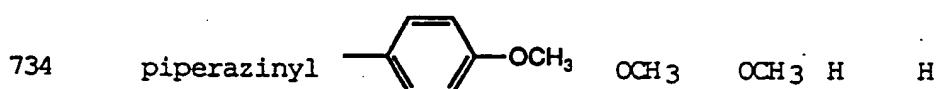
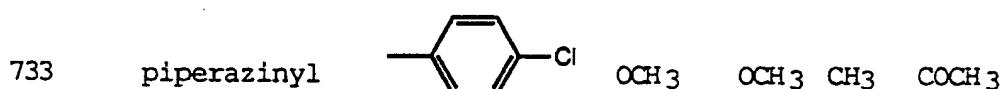
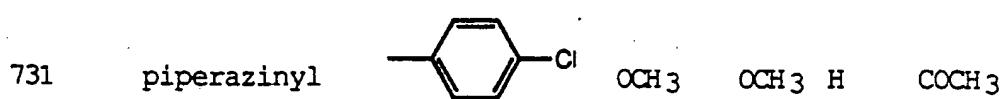
EXAMPLE NO.	L	R ¹³⁰	R ¹³¹	R ¹³²	E	P
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- 715 piperazinyl  OCH₃ OCH₃ H COCH₃
- 716 piperazinyl  OCH₃ OCH₃ CH₃ H
- 717 piperazinyl  OCH₃ OCH₃ CH₃ COCH₃
- 718 piperazinyl  OCH₃ OCH₃ OCH₃ H H
- 719 piperazinyl  OCH₃ OCH₃ OCH₃ H COCH₃
- 720 piperazinyl  OCH₃ OCH₃ OCH₃ CH₃ H
- 721 piperazinyl  OCH₃ OCH₃ OCH₃ CH₃ COCH₃

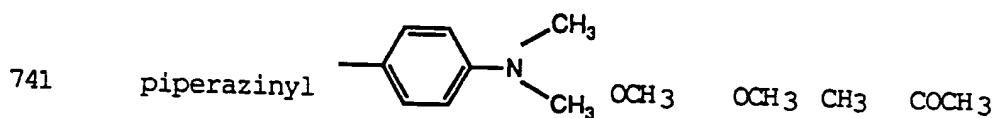
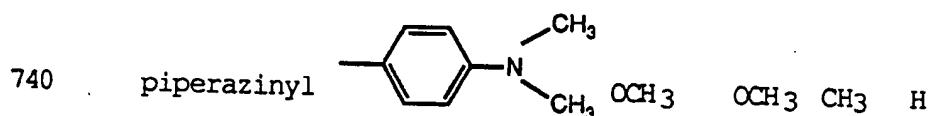
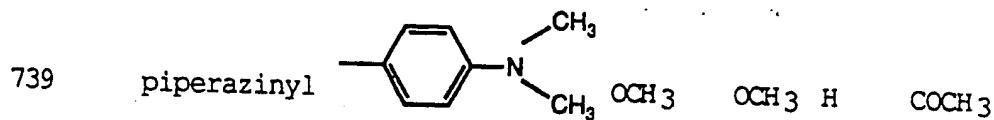
EXAMPLE NO.	L	R ¹³⁰	R ¹³¹	R ¹³²	E	P
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- 722 piperazinyl  OCH₃ OCH₃ H H
- 723 piperazinyl  OCH₃ OCH₃ H COCH₃
- 724 piperazinyl  OCH₃ OCH₃ CH₃ H
- 725 piperazinyl  OCH₃ OCH₃ CH₃ COCH₃
- 726 piperazinyl  OH OH H H
- 727 piperazinyl  OH OH H COCH₃
- 728 piperazinyl  OH OH CH₃ H
- 729 piperazinyl  OH OH CH₃ COCH₃
- 730 piperazinyl  OCH₃ OCH₃ H H

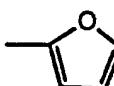
EXAMPLE NO.	L	R130	R131	R132	E	P
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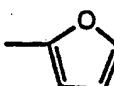


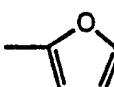
EXAMPLE NO.	L	R130	R131	R132	E	P
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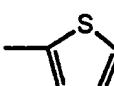


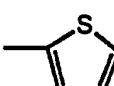
EXAMPLE NO.	L	R ¹³⁰	R ¹³¹	R ¹³²	E	P
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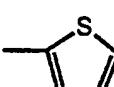
747 piperazinyl  OCH₃ OCH₃ H COCH₃

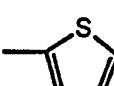
748 piperazinyl  OCH₃ OCH₃ CH₃ H

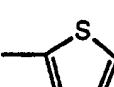
749 piperazinyl  OCH₃ OCH₃ CH₃ COCH₃

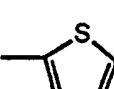
750 piperazinyl  OCH₃ OCH₃ H H

751 piperazinyl  OCH₃ OCH₃ H COCH₃

752 piperazinyl  OCH₃ OCH₃ CH₃ H

753 piperazinyl  OCH₃ OCH₃ CH₃ COCH₃

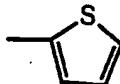
754 piperazinyl  OH OH H H

755 piperazinyl  OH OH H COCH₃

EXAMPLE NO.	L	R130	R131	R132	E	P
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756

piperazinyl



OH

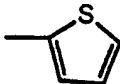
OH

CH₃

H

757

piperazinyl

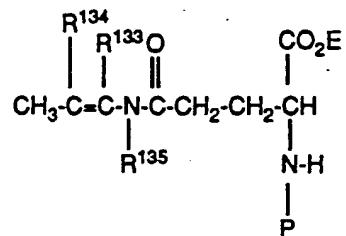


OH

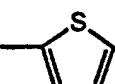
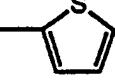
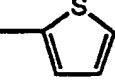
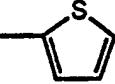
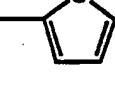
OH

CH₃COCH₃

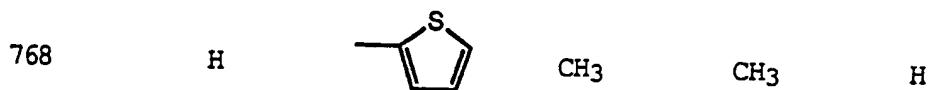
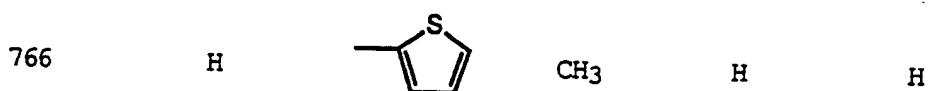
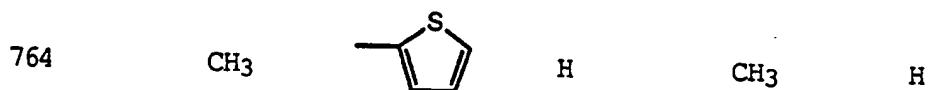
The following Examples #758-#809 of Table X are highly preferred conjugates composed of dopa-decarboxylase inhibitor compounds and glutamic acid derivatives. These dopa-decarboxylase inhibitors utilized to make these conjugates are propenoic acid derivatives based on the list of similar compounds described earlier.

TABLE X

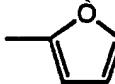
EXAMPLE NO.	R ¹³³	R ¹³⁴	R ¹³⁵	E	P
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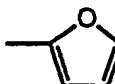
758	H		H	H	H
759	H		H	H	COCH ₃
760	H		H	CH ₃	H
761	H		H	CH ₃	COCH ₃
762	CH ₃		H	H	H

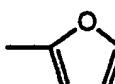
EXAMPLE NO.	R133	R134	R135	E	P
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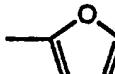


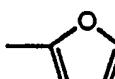
EXAMPLE NO.	R133	R134	R135	E	P
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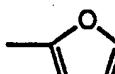
771 H  H H COCH₃

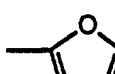
772 H  H CH₃ H

773 H  H CH₃ COCH₃

774 CH₃  H H H

775 CH₃  H H COCH₃

776 CH₃  H CH₃ H

777 CH₃  H CH₃ COCH₃

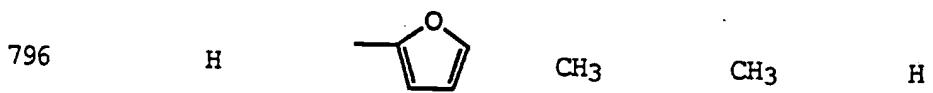
EXAMPLE NO.	R ¹³³	R ¹³⁴	R ¹³⁵	E	P
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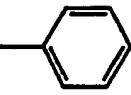
EXAMPLE NO.	R ¹³³	R ¹³⁴	R ¹³⁵	E	P
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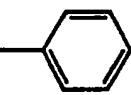


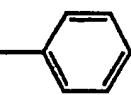
EXAMPLE NO.	R133	R134	R135	E	P
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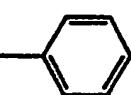


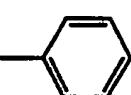
EXAMPLE NO.	R ¹³³	R ¹³⁴	R ¹³⁵	E	P
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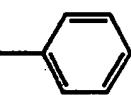
799 H  H H COCH₃

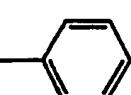
800 H  H CH₃ H

801 H  H CH₃ COCH₃

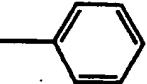
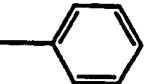
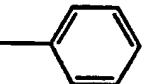
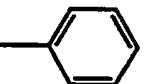
802 CH₃  H H H

803 CH₃  H H COCH₃

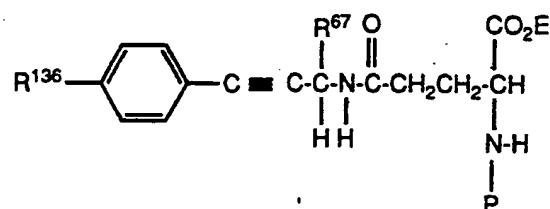
804 CH₃  H CH₃ H

805 CH₃  H CH₃ COCH₃

EXAMPLE NO.	R ¹³³	R ¹³⁴	R ¹³⁵	E	P
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806	H		CH ₃	H	H
807	H		CH ₃	H	COCH ₃
808	H		CH ₃	CH ₃	H
809	H		CH ₃	CH ₃	COCH ₃

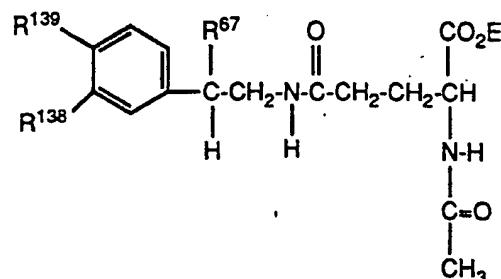
The following Examples #810-#833 of Table XI are highly preferred conjugates composed of dopa-decarboxylase inhibitor compounds and glutamic acid derivatives. These dopa-decarboxylase inhibitors utilized to make these conjugates are embraced by generic Formula IX, above.

TABLE XI

EXAMPLE NO.	R ⁶⁷	R ¹³⁶	E	P
810	H	H	H	H
811	H	H	H	COCH ₃
812	H	H	CH ₃	H
813	H	H	CH ₃	COCH ₃
814	H	OH	H	H
815	H	OH	H	COCH ₃
816	H	OH	CH ₃	H
817	H	OH	CH ₃	COCH ₃
818	H	OCH ₃	H	H
819	H	OCH ₃	H	COCH ₃
820	H	OCH ₃	CH ₃	H
821	H	OCH ₃	CH ₃	COCH ₃
822	CH ₃	H	H	H

EXAMPLE NO.	R ⁶⁷	R ¹³⁶	E	P
823	CH ₃	H	H	COCH ₃
824	CH ₃	H	CH ₃	H
825	CH ₃	H	CH ₃	COCH ₃
826	CH ₃	OH	H	H
827	CH ₃	OH	H	COCH ₃
828	CH ₃	OH	CH ₃	H
829	CH ₃	OH	CH ₃	COCH ₃
830	CH ₃	OCH ₃	H	H
831	CH ₃	OCH ₃	H	COCH ₃
832	CH ₃	OCH ₃	CH ₃	H
833	CH ₃	OCH ₃	CH ₃	COCH ₃

The following Examples #834-#857 of Table XII are highly preferred conjugates composed of dopa-decarboxylase inhibitor compounds and glutamic acid derivatives. These dopa-decarboxylase inhibitors utilized to make these conjugates are embraced by generic Formula IX, above.

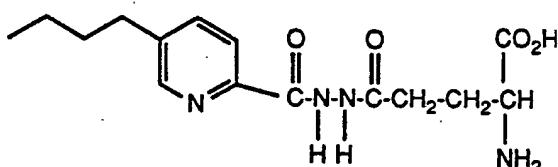
TABLE XII

EXAMPLE NO.	R ¹³⁸	R ¹³⁹	R ⁶⁷	E	P
834	H	H	C≡CH	H	H
835	H	H	C≡CH	H	COCH ₃
836	H	H	C≡CH	CH ₃	H
837	H	H	C≡CH	CH ₃	COCH ₃
838	OH	H	C≡CH	H	H
839	OH	H	C≡CH	H	COCH ₃
840	OH	H	C≡CH	CH ₃	H
841	OH	H	C≡CH	CH ₃	COCH ₃
842	H	OH	C≡CH	H	H
843	H	OH	C≡CH	H	COCH ₃
844	H	OH	C≡CH	CH ₃	H

EXAMPLE NO.	R ¹³⁸	R ¹³⁹	R ⁶⁷	E	P
845	H	OH	C≡CH	CH ₃	COCH ₃
846	H	H	CH=CH ₂	H	H
847	H	H	CH=CH ₂	H	COCH ₃
848	H	H	CH=CH ₂	CH ₃	H
849	H	H	CH=CH ₂	CH ₃	COCH ₃
850	OH	H	CH=CH ₂	H	H
851	OH	H	CH=CH ₂	H	COCH ₃
852	OH	H	CH=CH ₂	CH ₃	H
853	OH	H	CH=CH ₂	CH ₃	COCH ₃
854	H	OH	CH=CH ₂	H	H
855	H	OH	CH=CH ₂	H	COCH ₃
856	H	OH	CH=CH ₂	CH ₃	H
857	H	OH	CH=CH ₂	CH ₃	COCH ₃

The following Examples #858-#1857 comprise five classes of highly preferred conjugates composed of dopamine- β -hydroxylase inhibitor compounds and glutamic acid derivatives. Examples #858-#863 are descriptions of specific preparations of such conjugates. Examples #864-#1857, as shown in Tables XIII-XVII, may be prepared by procedures shown in these specific examples and in the foregoing general synthetic procedures of Schemes 1-7.

10

Example 858

L-glutamic acid, 5-[5-butyl-2-pyridinyl]carbonyl-hydrazide

15

Step. 1: Preparation of 5-n-Butylpicolinic (Fusaric) Acid Hydrazide.

A solution of 36.0 g (0.20 mol) of fusaric acid (Sigma) in 800 ml of absolute methanol was cooled to -10°C by means of an ice/methanol bath and 120 ml (199 g, 1.67 mol) of SOCl_2 was added dropwise over a 1 hr period. The reaction was allowed to slowly warm to ambient temperature and then stirred at reflux for 72 hr. The reaction was concentrated; the addition of 100 ml of toluene (twice) followed by reconcentration insured the complete removal of any unreacted SOCl_2 . The viscous syrup thus formed was dried in vacuo (0.01mm) overnight prior to treatment with cold NaHCO_3 (sat). The ester was extracted with ether and dried (MgSO_4). Concentration gave 32.3 g (83%) of crude methyl fusarate which was redissolved in 100 ml of absolute methanol and cooled to 0°C. Under a nitrogen atmosphere, 5.5 ml (0.174 mol) of anhydrous hydrazine was slowly added by syringe. The reaction was allowed to slowly warm to ambient temperature and stir

overnight. The methanol was removed and the yellow-brown residue was dried in vacuo (0.01 mm) overnight where it solidified producing 31.7g (98%) based on ester) of crude hydrazide.

Recrystallization from ether/hexane gave colorless needles: mp 5 51-53°C NMR (CDCl_3) δ 0.95 (t, $J = 7$ Hz, 3H, CH_2CH_3); 1.30-1.45 (m, 2H, CH_2CH_3); 1.55-1.70 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$); 2.67 (t, $J = 7$ Hz, 2H, ArCH_2); 7.65 (d of d, $J_{3,4} = 7$ Hz and $J_{4,6} = 2$ Hz, 1H, ArH); 8.05 (d, $J_{3,4} = 7$ Hz, 1H, ArH); 8.37 (d, 1H, ArH, $J_{4,6} = 2$ Hz); HRMS. Calcd for M + H: 194.1270. Found: 194.1293.

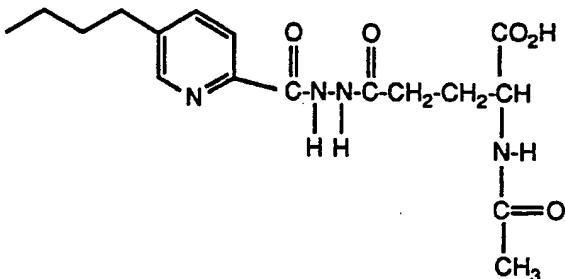
10

Step 2: Preparation of L-glutamic acid, 5-[5-(5-butyl-2-pyridinyl)carbonyl]hydrazide.

15 A solution of 7.27 g (24.0 mmol) of Boc-L- γ glutamic acid- α -t-butyl ester (BACHEM) in 150 ml of anhydrous THF was cooled to 0°C under static nitrogen and treated with 2.7 ml (2.46 g, 24.4 mmol) of anhydrous N-methyl morpholine. The mixture was then slowly treated with 3.1 ml (3.26 g, 23.9 mmol) of isobutyl chloroformate and allowed to stir for 1 hr prior to the dropwise 20 addition of a solution of 3.86 g (20.0 mmol) of fusaric acid hydrazide from step 1 in 30 ml of anhydrous THF. The reaction mixture was stirred at 0°C for 2 hr and then allowed to warm to ambient temperature and stir overnight. The N-methylmorpholine hydrochloride was removed by filtration and the filtrate 25 concentrated in vacuo to give 11.5 g of crude product which was a colorless glass. This material was dissolved in 50 ml of CH_2Cl_2 and treated with 50 ml of $\text{CF}_3\text{CO}_2\text{H}$. After 4 hr at ambient temperataure, the volitiles were removed in vacuo. The addition 30 of acetonitrile caused the product to precipitate producing 3.97 g (46%) of colorless material: mp 162-164°C (dec.); NMR (DMSO-d_6) δ 1.90 (t, $J = 7$ Hz, 3H, CH_2CH_3); 1.30-1.45 (m, 2H, CH_2CH_3); 1.50-1.65 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$); 2.00-2.20 (m, 1H, CH_2CH); 2.30-2.50 (m, 1H, CH_2CH); 2.70 (t, $J = 7$ Hz, 2H, ArCH_2); 3.60 (t, $J = 7$ Hz, 2H, COCH_2); 3.95-4.05 (M, 1H, CH_2CH); 7.85 (d of d, $J_{3,4} = 7$ Hz

and $\delta_{4,6}$ = 2 Hz, 1H, ArH); 7.95 (d, $\delta_{3,4}$ = 7 Hz, 1H, ArH); 8.55 (d, $\delta_{4,6}$ = 2 Hz, 1H, ArH).

5

Example 859

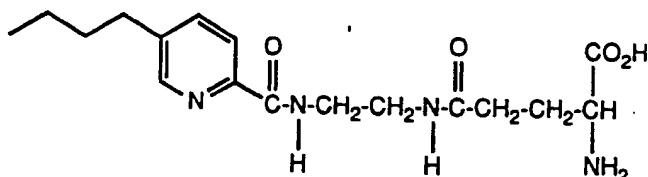
10 N-acetyl-L-glutamic acid, 5-[1-(5-butyl-2-pyridinyl)-carbonyl]hydrazide

A suspension of 2.85 g (6.54 mmol) of the compound of Example 858 in CH₃CN/H₂O (1:1) was treated with 2 equiv. of 1 M K₂CO₃ at 0°C. With efficient stirring, 1 ml (10.6 mmol) of acetic anhydride and 11 ml (11 mmol) of 1M K₂CO₃ were added every 10 min for 1 hr; since the product is soluble, the mixture became homogenous as the reaction proceeded. The reaction mixture was stirred for 1 hr, filtered, and the filtrate cooled to 0°C. The pH was adjusted to pH 4 by the careful addition of cold dilute HCl. All volitiles were removed in vacuo and the product dissolved in ethanol. Recrystallization from ethanol/petroleum ether produced 2.16g (69%) of colorless material: mp 191.5-192.0°C; NMR (D₂O and NaOD) δ 1.85 (t, δ = 7 Hz, 3H, CH₂CH₃); 1.20-1.35 (m, 2H, CH₂CH₃); 1.55-1.70 (m, 2H, CH₂CH₂CH₂); 1.95-2.10 (m, 1H, CH₂CH); 2.05 (s, 3H, COCH₃); 2.20-2.35 (m, 1H, CH₂CH); 2.45 (t, δ = 7 Hz, 2H, COCH₂); 2.75 (t, 2H, ArCH₂); 3.45-3.55 (m, 1H, CH₂CH); 8.05 (s, 2H, ArH); 8.55 (s, 1H, ArH); HRMS. Calcd for M + H: 365.1825. Found 365.1860.

Anal.

Calcd. for C₁₇H₂₄N₄O₅: C, 55.98; H, 6.58; N, 15.36. Found: C, 55.96; H, 6.64; N, 15.30.

5

Example 860

N-[2-[[5-butyl-2-pyridinyl]carbonyl]amino]ethyl-L-glutamine.

10

Step 1: Preparation of the ethylene diamine amide of fusaric acid.

A solution of 7.8 g (130 mmol) of ethylene diamine in
15 400 mL of anhydrous THF under nitrogen was treated with 27 mmol
of n-butyllithium at 0°C. The solution was allowed to stir for
30 min and was treated with 5.0 g (26 mmol) of neat methyl
fusarate (from step 1 of Example 690) by syringe. The reaction
was kept at 0°C for 2 hr and stirred at ambient temperature
20 overnight. The reaction was quenched with water, filtered, and
concentrated in vacuo. Purification by silica gel chromatography
gave 3.8 g (66%) of pure amide: NMR (DMSO-d₆) δ 0.90 (t, J = 8
Hz, 3H), 1.23-1.38 (m, 2H), 1.52-1.64 (m, 2H), 2.67 (t, J = 8 Hz,
2H), 2.74 (t, J = 8 Hz, 2H), 3.18-3.30 (br s, 2H), 3.34 (q, J = 8
Hz, 2H), 7.82 d of d, J = 9 Hz and 2 Hz, 1H), 7.96 (d, J = 9 Hz,
25 1H), 8.47 (d, J = 2 Hz, 1H), 8.75 (t, J = 8 Hz, 1H).

30

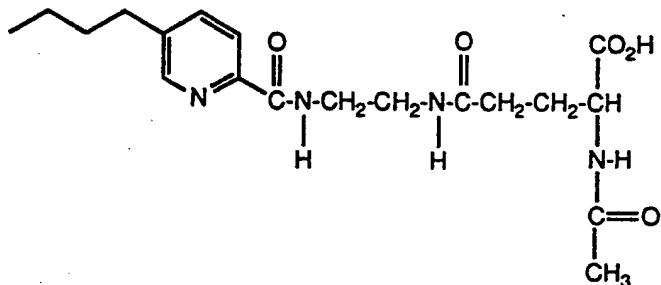
Step 2: Preparation of N-[2-[[5-butyl-2-
pyridinyl]carbonyl]aminolethyll-L-glutmine.

Under nitrogen, a solution of 26.8 g (88.5 mmol) of N-Boc-L-γ-glutamic acid-α-t-butyl ester (BACHEM) in 125 mL of

methylene chloride was treated with 9.14 g (44.3 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction was allowed to stir for 2 hr prior to filtration under a nitrogen atmosphere. The anhydride solution was slowly added to a solution of 8.5 g (38.5 mmol) of the ethylene diamine amide from step 1 in 100 mL of methylene chloride. The reaction was allowed to stir overnight and was concentrated in vacuo. The residue was dissolved in ethyl acetate, washed with 1M K₂CO₃ followed by water, dried (MgSO₄) and reconcentrated in vacuo to give the protected coupled product; a solution of this material in 250 mL of methylene chloride was cooled to 0°C and treated with 250 mL of trifluoroacetic acid (TFA). The reaction was allowed to warm to ambient temperature and stir overnight; the course of the reaction was monitored by analytical LC. Concentration in vacuo gave N-[2-[[[5-butyl-2-pyridinyl]carbonyl]amino]ethyl]-L-glutamine.

Example 861

20



N2-acetyl-N-[2-[[[5-butyl-2-pyridinyl]carbonyl]amino]ethyl]-L-glutamine.

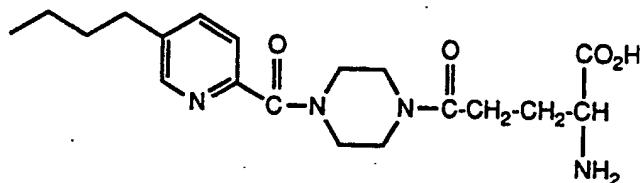
The compound of Example 860 was dissolved in 150 mL of acetonitrile/water (1:1) and the pH adjusted to 9 with 2 M K₂CO₃. The solution was cooled to 0°C and 2.27 mL (24 mmol) of acetic anhydride and 12 mL (24 mmol) of 2 M K₂CO₃ was added every 30

min. for 5 h; the pH was maintained at 9 and the reaction temperature kept below 5°C. After the last addition, the reaction was allowed to warm to ambient temperature overnight. The pH was adjusted to 3 with 3 M HCl and concentrated to 300 mL.

- 5 Purification by reverse phase chromatography (Waters Deltaprep-3000) using isocratic 30% acetonitrile/water (0.05% TFA) gave 7.8 g (52% overall yield from the amide of step 1) of colorless product; an analytical sample was recrystallized from acetonitrile and then water: mp 156-158°C; Anal. Calcd for
 10 $C_{19}H_{28}N_4O_5 \cdot 0.83$ TFA: C, 57.32; H, 7.00; N, 13.96; F, 1.14%. Found: C, 57.22; H, 7.07; N, 13.88; F, 1.07.

Example 862

15



2-amino-5-[4-[(5-butyl-2-pyridinyl)carbonyl]-1-piperazinyl]-5-oxopentanoic acid.

20

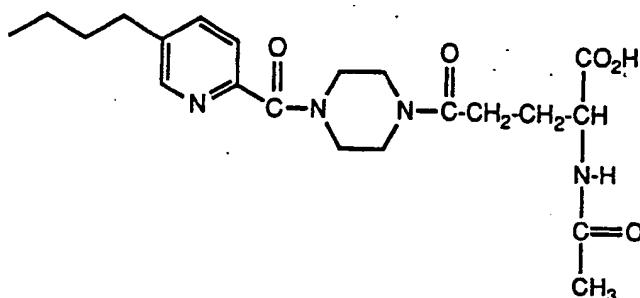
Step 1: Preparation of the piperazine amide of fusaric acid.

- A solution of 11.20 g (130 mmol) of piperazine in 400 mL of anhydrous THF under nitrogen was treated with 27.3 mmol of n-butyllithium at 0°C. The solution was allowed to stir for 30 min and was treated with 5.0 g (26 mmol) of neat methyl fusarate (from step 1 of Example 690) by syringe. The reaction was kept at 0°C for 2 hr and stirred at ambient temperature overnight. The reaction was quenched with water, filtered, and concentrated in vacuo. Purification by silica gel chromatography using chloroform/methanol (70:30) gave 5.82 g (90%) of pure amide: NMR ($CDCl_3$) δ 0.94 (t, J = 8 Hz, 3H), 1.28-1.45 (m, 2H), 1.55-1.67 (m, 2H), 1.66-1.72 (br s, 1H), 2.64 (t, J = 8 Hz, 2H), 2.86 (t, J = 6

Hz, 2H), 2.97 (t, J = 6 Hz, 2H), 3.58 (t, J = 6 Hz, 2H) 3.77 (t, J = 6 Hz, 2H), 7.54-7.63 (m, 2H), 8.37-8.43 (br s, 1H).

Step 2: Preparation of 2-amino-5-[4-[5-butyl-2-
5 pyridinyl]carbonyl]-1-piperazinyl]-5-oxopentanoic acid.

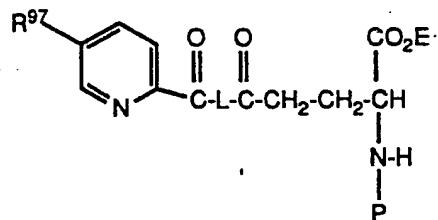
Under nitrogen, a solution of 17.4 g (57 mmol) of N-Boc-L- γ -glutamic acid- α -t-butyl ester (BACHEM) in 100 mL of anhydrous THF was treated with 5.57 g (27 mmol) of solid 10 dicyclohexylcarbodiimide (DCC). The reaction was allowed to stir for 2 hr prior to filtration under a nitrogen atmosphere. The anhydride solution was slowly added to a solution of 5.82 g (23.5 mmol) of the piperazine amide from step 1 in 50 mL of anhydrous THF. The reaction was allowed to stir overnight and was 15 concentrated in vacuo. The residue was dissolved in ethyl acetate, washed with 1M K₂CO₃ followed by water, dried (MgSO₄), and reconcentrated in vacuo to give the protected coupled product; a solution of this material in 150 mL of methylene chloride was cooled to 0°C and treated with 150 mL of 20 trifluoroacetic acid (TFA) under nitrogen. The reaction was allowed to warm to ambient temperature and stir overnight; the course of the reaction was monitored by analytical LC. Concentration in vacuo gave 2-amino-5-[4-[5-butyl-2-pyridinyl]carbonyl]-1-piperazinyl]-5-oxopentanoic acid.

Example 863

- 5 2-(acetylamino)-5-(4-[(5-butyl-2-pyridinyl)carbonyl]-1-piperazinyl)-5-oxopentanoic acid.

The compound of Example 862 was dissolved in 150 mL of acetonitrile/water (1:1) and the pH adjusted to 9 with 1 M K₂CO₃.
 10 The solution was cooled to 0°C and 2.36 mL (25 mmol) of acetic anhydride and 25 mL (25 mmol) of 1 M K₂CO₃ was added every 30 min. for 5 h; the pH was maintained at 9 and the reaction temperature kept below 5°C. After the last addition, the reaction was allowed to warm to ambient temperature overnight.
 15 The pH was adjusted to 4 with 3 M HCl and concentrated to 300 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) using isocratic 25% acetonitrile/water (0.05% TFA) gave 8.13 g (78%) of colorless product: MS (FAB) m/e (rel intensity) 419 (100), 258 (10), 248 (37), 205 (28); HRMS. Calcd for M+H:
 20 419.2294. Found: 419.2250.

The following Examples #864-#1097 of Table XIII are highly preferred conjugates composed of dopamine-β-hydroxylase inhibitor compounds and glutamic acid derivatives. These dopamine-β-hydroxylase inhibitors utilized to make these conjugates are embraced by generic Formula XIV and XV, above.

TABLE XIII

EXAMPLE NO.	L	R ⁹⁷	E	P
864	NHNH	C ₂ H ₅	CH ₃	H
865	NHNH	C ₂ H ₅	CH ₃	COCH ₃
866	NHNH	C ₃ H ₇	H	H
867	NHNH	C ₃ H ₇	H	COCH ₃
868	NHNH	C ₃ H ₇	CH ₃	H
869	NHNH	C ₃ H ₇	CH ₃	COCH ₃
870	NHNH	CH ₃	H	H
871	NHNH	CH ₃	H	COCH ₃
872	NHNH	C ₄ H ₉	CH ₃	H
873	NHNH	C ₄ H ₉	CH ₃	COCH ₃
874	NHNH	C ₅ H ₁₁	H	H
875	NHNH	C ₅ H ₁₁	H	COCH ₃

EXAMPLE NO.	L	R ⁹⁷	E	P
876	NHNH	C ₅ H ₁₁	CH ₃	H
877	NHNH	C ₅ H ₁₁	CH ₃	COCH ₃
878	NHNH	C ₆ H ₁₃	H	H
879	NHNH	C ₆ H ₁₃	H	COCH ₃
880	NHNH	C ₆ H ₁₃	CH ₃	H
881	NHNH	C ₆ H ₁₃	CH ₃	COCH ₃
882	NHNH	OCH ₃	H	H
883	NHNH	OCH ₃	H	COCH ₃
884	NHNH	OCH ₃	CH ₃	H
885	NHNH	OCH ₃	CH ₃	COCH ₃
886	NHNH	OC ₂ H ₅	H	H
887	NHNH	OC ₂ H ₅	H	COCH ₃
888	NHNH	OC ₂ H ₅	CH ₃	H
889	NHNH	OC ₂ H ₅	CH ₃	COCH ₃
890	NHNH	OC ₃ H ₇	H	H
891	NHNH	OC ₃ H ₇	H	COCH ₃

EXAMPLE NO.	L	R ⁹⁷	E	P
892	NHNH	OC ₃ H ₇	CH ₃	H
893	NHNH	OC ₃ H ₇	CH ₃	COCH ₃
894	NHNH	OC ₄ H ₉	H	H
895	NHNH	OC ₄ H ₉	H	COCH ₃
896	NHNH	OC ₄ H ₉	CH ₃	H
897	NHNH	OC ₄ H ₉	CH ₃	COCH ₃
898	NHNH	SCH ₃	H	H
899	NHNH	SCH ₃	H	COCH ₃
900	NHNH	SCH ₃	CH ₃	H
901	NHNH	SCH ₃	CH ₃	COCH ₃
902	NHNH	SC ₂ H ₅	H	H
903	NHNH	SC ₂ H ₅	H	COCH ₃
904	NHNH	SC ₂ H ₅	CH ₃	H
905	NHNH	SC ₂ H ₅	CH ₃	COCH ₃
906	NHNH	SC ₃ H ₇	H	H
907	NHNH	SC ₃ H ₇	H	COCH ₃

EXAMPLE NO.	L	R ⁹⁷	E	P
908	NHNH	SC ₃ H ₇	CH ₃	H
909	NHNH	SC ₃ H ₇	CH ₃	COCH ₃
910	NHNH	F	H	H
911	NHNH	F	H	COCH ₃
912	NHNH	F	CH ₃	H
913	NHNH	F	CH ₃	COCH ₃
914	NHNH	Cl	H	H
915	NHNH	Cl	H	COCH ₃
916	NHNH	Cl	CH ₃	H
917	NHNH	Cl	CH ₃	COCH ₃
918	NHNH	Br	H	H
919	NHNH	Br	H	COCH ₃
920	NHNH	Br	CH ₃	H
921	NHNH	Br	CH ₃	COCH ₃
922	NHNH	I	H	H
923	NHNH	I	H	COCH ₃

EXAMPLE NO.	L	R ⁹⁷	E	P
924	NHNH	I	CH ₃	H
925	NHNH	I	CH ₃	COCH ₃
926	NHNH	CN	H	H
927	NHNH	CN	H	COCH ₃
928	NHNH	CN	CH ₃	H
929	NHNH	CN	CH ₃	COCH ₃
930	NHNH	NO ₂	H	H
931	NHNH	NO ₂	H	COCH ₃
932	NHNH	NO ₂	CH ₃	H
933	NHNH	NO ₂	CH ₃	COCH ₃
934	NHNH	OH	H	H
935	NHNH	OH	H	COCH ₃
936	NHNH	OH	CH ₃	H
937	NHNH	OH	CH ₃	COCH ₃
938	NHCH ₂ CH ₂ NH	CH ₃	H	H
939	NHCH ₂ CH ₂ NH	CH ₃	H	COCH ₃

EXAMPLE NO.	L	R ⁹⁷	E	P
940	NHCH ₂ CH ₂ NH	CH ₃	CH ₃	H
941	NHCH ₂ CH ₂ NH	CH ₃	CH ₃	COCH ₃
942	NHCH ₂ CH ₂ NH	C ₂ H ₅	H	H
943	NHCH ₂ CH ₂ NH	C ₂ H ₅	H	COCH ₃
944	NHCH ₂ CH ₂ NH	C ₂ H ₅	CH ₃	H
945	NHCH ₂ CH ₂ NH	C ₂ H ₅	CH ₃	COCH ₃
946	NHCH ₂ CH ₂ NH	C ₃ H ₇	H	H
947	NHCH ₂ CH ₂ NH	C ₃ H ₇	H	COCH ₃
948	NHCH ₂ CH ₂ NH	C ₃ H ₇	CH ₃	H
949	NHCH ₂ CH ₂ NH	C ₃ H ₇	CH ₃	COCH ₃
950	NHNH	CH ₃	CH ₃	CH ₃
951	NHNH	CH ₃	CH ₃	COCH ₃
952	NHCH ₂ CH ₂ NH	C ₄ H ₉	CH ₃	H
953	NHCH ₂ CH ₂ NH	C ₄ H ₉	CH ₃	COCH ₃
954	NHCH ₂ CH ₂ NH	C ₅ H ₁₁	H	H
955	NHCH ₂ CH ₂ NH	C ₅ H ₁₁	H	COCH ₃

EXAMPLE NO.	L	R ⁹⁷	E	P
956	NHCH ₂ CH ₂ NH	C ₅ H ₁₁	CH ₃	H
957	NHCH ₂ CH ₂ NH	C ₅ H ₁₁	CH ₃	COCH ₃
958	NHCH ₂ CH ₂ NH	C ₆ H ₁₃	H	H
959	NHCH ₂ CH ₂ NH	C ₆ H ₁₃	H	COCH ₃
960	NHCH ₂ CH ₂ NH	C ₆ H ₁₃	CH ₃	H
961	NHCH ₂ CH ₂ NH	C ₆ H ₁₃	CH ₃	COCH ₃
962	NHCH ₂ CH ₂ NH	OCH ₃	H	H
963	NHCH ₂ CH ₂ NH	OCH ₃	H	COCH ₃
964	NHCH ₂ CH ₂ NH	OCH ₃	CH ₃	H
965	NHCH ₂ CH ₂ NH	OCH ₃	CH ₃	COCH ₃
966	NHCH ₂ CH ₂ NH	OC ₂ H ₅	H	H
967	NHCH ₂ CH ₂ NH	OC ₂ H ₅	H	COCH ₃
968	NHCH ₂ CH ₂ NH	OC ₂ H ₅	CH ₃	H
969	NHCH ₂ CH ₂ NH	OC ₂ H ₅	CH ₃	COCH ₃
970	NHCH ₂ CH ₂ NH	OC ₃ H ₇	H	H
971	NHCH ₂ CH ₂ NH	OC ₃ H ₇	H	COCH ₃

EXAMPLE NO.	L	R ⁹⁷	E	P
972	NHCH ₂ CH ₂ NH	OC ₃ H ₇	CH ₃	H
973	NHCH ₂ CH ₂ NH	OC ₃ H ₇	CH ₃	COCH ₃
974	NHCH ₂ CH ₂ NH	OC ₄ H ₉	H	H
975	NHCH ₂ CH ₂ NH	OC ₄ H ₉	H	COCH ₃
976	NHCH ₂ CH ₂ NH	OC ₄ H ₉	CH ₃	H
977	NHCH ₂ CH ₂ NH	OC ₄ H ₉	CH ₃	COCH ₃
978	NHCH ₂ CH ₂ NH	SCH ₃	H	H
979	NHCH ₂ CH ₂ NH	SCH ₃	H	COCH ₃
980	NHCH ₂ CH ₂ NH	SCH ₃	CH ₃	H
981	NHCH ₂ CH ₂ NH	SCH ₃	CH ₃	COCH ₃
982	NHCH ₂ CH ₂ NH	SC ₂ H ₅	H	H
983	NHCH ₂ CH ₂ NH	SC ₂ H ₅	H	COCH ₃
984	NHCH ₂ CH ₂ NH	SC ₂ H ₅	CH ₃	H
985	NHCH ₂ CH ₂ NH	SC ₂ H ₅	CH ₃	COCH ₃
986	NHCH ₂ CH ₂ NH	SC ₃ H ₇	H	H
987	NHCH ₂ CH ₂ NH	SC ₃ H ₇	H	COCH ₃

EXAMPLE NO.	L	R ⁹⁷	E	P
988	NHCH ₂ CH ₂ NH	SC ₃ H ₇	CH ₃	H
989	NHCH ₂ CH ₂ NH	SC ₃ H ₇	CH ₃	COCH ₃
990	NHCH ₂ CH ₂ NH	F	H	H
991	NHCH ₂ CH ₂ NH	F	H	COCH ₃
992	NHCH ₂ CH ₂ NH	F	CH ₃	H
993	NHCH ₂ CH ₂ NH	F	CH ₃	COCH ₃
994	NHCH ₂ CH ₂ NH	Cl	H	H
995	NHCH ₂ CH ₂ NH	Cl	H	COCH ₃
996	NHCH ₂ CH ₂ NH	Cl	CH ₃	H
997	NHCH ₂ CH ₂ NH	Cl	CH ₃	COCH ₃
998	NHCH ₂ CH ₂ NH	Br	H	H
999	NHCH ₂ CH ₂ NH	Br	H	COCH ₃
1000	NHCH ₂ CH ₂ NH	Br	CH ₃	H
1001	NHCH ₂ CH ₂ NH	Br	CH ₃	COCH ₃
1002	NHCH ₂ CH ₂ NH	I	H	H
1003	NHCH ₂ CH ₂ NH	I	H	COCH ₃

EXAMPLE NO.	L	R ⁹⁷	E	P
1004	NHCH ₂ CH ₂ NH	I	CH ₃	H
1005	NHCH ₂ CH ₂ NH	I	CH ₃	COCH ₃
1006	NHCH ₂ CH ₂ NH	CN	H	H
1007	NHCH ₂ CH ₂ NH	CN	H	COCH ₃
1008	NHCH ₂ CH ₂ NH	CN	CH ₃	H
1009	NHCH ₂ CH ₂ NH	CN	CH ₃	COCH ₃
1010	NHCH ₂ CH ₂ NH	NO ₂	H	H
1011	NHCH ₂ CH ₂ NH	NO ₂	H	COCH ₃
1012	NHCH ₂ CH ₂ NH	NO ₂	CH ₃	H
1013	NHCH ₂ CH ₂ NH	NO ₂	CH ₃	COCH ₃
1014	NHCH ₂ CH ₂ NH	OH	H	H
1015	NHCH ₂ CH ₂ NH	OH	H	COCH ₃
1016	NHCH ₂ CH ₂ NH	OH	CH ₃	H
1017	NHCH ₂ CH ₂ NH	OH	CH ₃	COCH ₃
1018	piperzinyl	CH ₃	H	H
1019	piperzinyl	CH ₃	H	COCH ₃

EXAMPLE NO.	L	R ⁹⁷	E	P
1020	piperzinyl	CH ₃	CH ₃	H
1021	piperzinyl	CH ₃	CH ₃	COCH ₃
1022	piperzinyl	C ₂ H ₅	H	H
1023	piperzinyl	C ₂ H ₅	H	COCH ₃
1024	piperzinyl	C ₂ H ₅	CH ₃	H
1025	piperzinyl	C ₂ H ₅	CH ₃	COCH ₃
1026	piperzinyl	C ₃ H ₇	H	H
1027	piperzinyl	C ₃ H ₇	H	COCH ₃
1028	piperzinyl	C ₃ H ₇	CH ₃	H
1029	piperzinyl	C ₃ H ₇	CH ₃	COCH ₃
1030	NHNH	C ₂ H ₅	H	H
1031	NHNH	C ₂ H ₅	H	COCH ₃
1032	piperzinyl	C ₄ H ₉	CH ₃	H
1033	piperzinyl	C ₄ H ₉	CH ₃	COCH ₃
1034	piperzinyl	C ₅ H ₁₁	H	H
1035	piperzinyl	C ₅ H ₁₁	H	COCH ₃

EXAMPLE NO.	L	R ⁹⁷	E	P
1036	piperzinyl	C ₅ H ₁₁	CH ₃	H
1037	piperzinyl	C ₅ H ₁₁	CH ₃	COCH ₃
1038	piperzinyl	C ₆ H ₁₃	H	H
1039	piperzinyl	C ₆ H ₁₃	H	COCH ₃
1040	piperzinyl	C ₆ H ₁₃	CH ₃	H
1041	piperzinyl	C ₆ H ₁₃	CH ₃	COCH ₃
1042	piperzinyl	OCH ₃	H	H
1043	piperzinyl	OCH ₃	H	COCH ₃
1044	piperzinyl	OCH ₃	CH ₃	H
1045	piperzinyl	OCH ₃	CH ₃	COCH ₃
1046	piperzinyl	OC ₂ H ₅	H	H
1047	piperzinyl	OC ₂ H ₅	H	COCH ₃
1048	piperzinyl	OC ₂ H ₅	CH ₃	H
1049	piperzinyl	OC ₂ H ₅	CH ₃	COCH ₃
1050	piperzinyl	OC ₃ H ₇	H	H
1051	piperzinyl	OC ₃ H ₇	H	COCH ₃

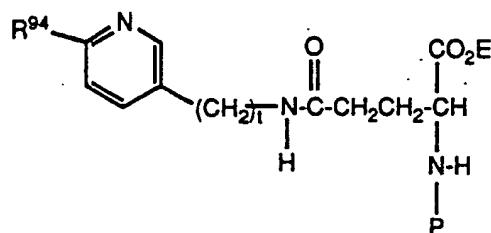
EXAMPLE NO.	L	R ⁹⁷	E	P
1052	piperziny1	OC ₃ H ₇	CH ₃	H
1053	piperziny1	OC ₃ H ₇	CH ₃	COCH ₃
1054	piperziny1	OC ₄ H ₉	H	H
1055	piperziny1	OC ₄ H ₉	H	COCH ₃
1056	piperziny1	OC ₄ H ₉	CH ₃	H
1057	piperziny1	OC ₄ H ₉	CH ₃	COCH ₃
1058	piperziny1	SCH ₃	H	H
1059	piperziny1	SCH ₃	H	COCH ₃
1060	piperziny1	SCH ₃	CH ₃	H
1061	piperziny1	SCH ₃	CH ₃	COCH ₃
1062	piperziny1	SC ₂ H ₅	H	H
1063	piperziny1	SC ₂ H ₅	H	COCH ₃
1064	piperziny1	SC ₂ H ₅	CH ₃	H
1065	piperziny1	SC ₂ H ₅	CH ₃	COCH ₃
1066	piperziny1	SC ₃ H ₇	H	H
1067	piperziny1	SC ₃ H ₇	H	COCH ₃

EXAMPLE NO.	L	R ⁹⁷	E	P
1068	piperziny1	SC ₃ H ₇	CH ₃	H
1069	piperziny1	SC ₃ H ₇	CH ₃	COCH ₃
1070	piperziny1	F	H	H
1071	piperziny1	F	H	COCH ₃
1072	piperziny1	F	CH ₃	H
1073	piperziny1	F	CH ₃	COCH ₃
1074	piperziny1	Cl	H	H
1075	piperziny1	Cl	H	COCH ₃
1076	piperziny1	Cl	CH ₃	H
1077	piperziny1	Cl	CH ₃	COCH ₃
1078	piperziny1	Br	H	H
1079	piperziny1	Br	H	COCH ₃
1080	piperziny1	Br	CH ₃	H
1081	piperziny1	Br	CH ₃	COCH ₃
1082	piperziny1	I	H	H
1083	piperziny1	I	H	COCH ₃

EXAMPLE NO.	L	R ⁹⁷	E	P
1084	piperzinyl	I	CH ₃	H
1085	piperzinyl	I	CH ₃	COCH ₃
1086	piperzinyl	CN	H	H
1087	piperzinyl	CN	H	COCH ₃
1088	piperzinyl	CN	CH ₃	H
1089	piperzinyl	CN	CH ₃	COCH ₃
1090	piperzinyl	NO ₂	H	H
1091	piperzinyl	NO ₂	H	COCH ₃
1092	piperzinyl	NO ₂	CH ₃	H
1093	piperzinyl	NO ₂	CH ₃	COCH ₃
1094	piperzinyl	OH	H	H
1095	piperzinyl	OH	H	COCH ₃
1096	piperzinyl	OH	CH ₃	H
1097	piperzinyl	OH	CH ₃	COCH ₃

EXAMPLE NO.	L	R ⁹⁷	E	P
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The following Examples #1098-#1137 of Table XIV are highly preferred conjugates composed of dopamine- β -hydroxylase inhibitor compounds and glutamic acid derivatives. These dopamine- β -hydroxylase inhibitors utilized to make these conjugates are embraced by generic Formula XIV, above.

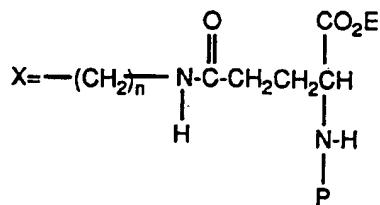
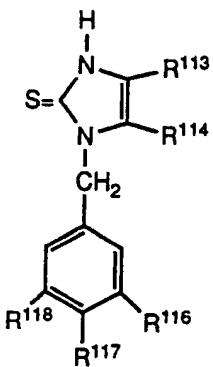
TABLE XIV

EXAMPLE NO.	R ⁹⁴	t	E	P
1098	CO ₂ H	0	H	H
1099	CO ₂ H	0	H	COCH ₃
1100	CO ₂ H	0	CH ₃	H
1101	CO ₂ H	0	CH ₃	COCH ₃
1102	CN ₄ H	0	H	H
1103	CN ₄ H	0	H	COCH ₃
1104	CN ₄ H	0	CH ₃	H
1105	CN ₄ H	0	CH ₃	COCH ₃
1106	CO ₂ H	1	H	H
1107	CO ₂ H	1	H	COCH ₃
1108	CO ₂ H	1	CH ₃	H
1109	CO ₂ H	1	CH ₃	COCH ₃

EXAMPLE NO.	R ⁹⁴	t	E	P
1110	CN ₄ H	1	H	H
1111	CN ₄ H	1	H	COCH ₃
1112	CN ₄ H	1	CH ₃	H
1113	CN ₄ H	1	CH ₃	COCH ₃
1114	CO ₂ H	2	H	H
1115	CO ₂ H	2	H	COCH ₃
1116	CO ₂ H	2	CH ₃	H
1117	CO ₂ H	2	CH ₃	COCH ₃
1118	CN ₄ H	2	H	H
1119	CN ₄ H	2	H	COCH ₃
1120	CN ₄ H	2	CH ₃	H
1121	CN ₄ H	2	CH ₃	COCH ₃
1122	CO ₂ H	3	H	H
1123	CO ₂ H	3	H	COCH ₃
1124	CO ₂ H	3	CH ₃	H
1125	CO ₂ H	3	CH ₃	COCH ₃

EXAMPLE NO.	R ⁹⁴	t	E	P
1126	CN ₄ H	3	H	H
1127	CN ₄ H	3	H	COCH ₃
1128	CN ₄ H	3	CH ₃	H
1129	CN ₄ H	3	CH ₃	COCH ₃
1130	CO ₂ H	4	H	H
1131	CO ₂ H	4	H	COCH ₃
1132	CO ₂ H	4	CH ₃	H
1133	CO ₂ H	4	CH ₃	COCH ₃
1134	CN ₄ H	4	H	H
1135	CN ₄ H	4	H	COCH ₃
1136	CN ₄ H	4	CH ₃	H
1137	CN ₄ H	4	CH ₃	COCH ₃

The following Examples #1138-#1377 of Table XV are highly preferred conjugates composed of dopamine- β -hydroxylase inhibitor compounds and glutamic acid derivatives. These dopamine- β -hydroxylase inhibitors utilized to make these conjugates are embraced by generic Formula XVIII, above.

TABLE XV

EXAMPLE NO.	n	R ¹¹	R ¹¹⁴	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1138	0	X	H	H	OH	H	H	H
1139	0	X	H	H	OH	H	H	COCH ₃
1140	0	X	H	H	OH	H	CH ₃	H
1141	0	X	H	H	OH	H	CH ₃	COCH ₃
1142	0	X	H	H	F	H	H	H
1143	0	X	H	H	F	H	H	COCH ₃
1144	0	X	H	H	F	H	CH ₃	H
1145	0	X	H	H	F	H	CH ₃	COCH ₃
1146	0	X	H	H	CF ₃	H	H	H
1147	0	X	H	H	CF ₃	H	H	COCH ₃
1148	0	X	H	H	CF ₃	H	CH ₃	H
1149	0	X	H	H	CF ₃	H	CH ₃	COCH ₃
1150	0	X	H	OH	OH	H	H	H
1151	0	X	H	OH	OH	H	H	COCH ₃

EXAMPLE NO.	n	R ¹¹	R ¹¹⁴	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1152	0	X	H	OH	OH	H	CH ₃	H
1153	0	X	H	OH	OH	H	CH ₃	COCH ₃
1154	0	X	H	F	H	F	H	H
1155	0	X	H	F	H	F	H	COCH ₃
1156	0	X	H	F	H	F	CH ₃	H
1157	0	X	H	F	H	F	CH ₃	COCH ₃
1158	0	X	H	CF ₃	H	CF ₃	H	H
1159	0	X	H	CF ₃	H	CF ₃	H	COCH ₃
1160	0	X	H	CF ₃	H	CF ₃	CH ₃	H
1161	0	X	H	CF ₃	H	CF ₃	CH ₃	COCH ₃
1162	0	H	X	H	OH	H	H	H
1163	0	H	X	H	OH	H	H	COCH ₃
1164	0	H	X	H	OH	H	CH ₃	H
1165	0	H	X	H	OH	H	CH ₃	COCH ₃
1166	0	H	X	H	F	H	H	H
1167	0	H	X	H	F	H	H	COCH ₃
1168	0	H	X	H	F	H	CH ₃	H
1169	0	H	X	H	F	H	CH ₃	COCH ₃
1170	0	H	X	H	CF ₃	H	H	H
1171	0	H	X	H	CF ₃	H	H	COCH ₃
1172	0	H	X	H	CF ₃	H	CH ₃	H
1173	0	H	X	H	CF ₃	H	CH ₃	COCH ₃
1174	0	H	X	OH	OH	H	H	H
1175	0	H	X	OH	OH	H	H	COCH ₃

EXAMPLE NO.	n	R ¹¹	R ¹¹⁴	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1176	0	H	X	OH	OH	H	CH ₃	H
1177	0	H	X	OH	OH	H	CH ₃	COCH ₃
1178	0	H	X	F	H	F	H	H
1179	0	H	X	F	H	F	H	COCH ₃
1180	0	H	X	F	H	F	CH ₃	H
1181	0	H	X	F	H	F	CH ₃	COCH ₃
1182	0	H	X	CF ₃	H	CF ₃	H	H
1183	0	H	X	CF ₃	H	CF ₃	H	COCH ₃
1184	0	H	X	CF ₃	H	CF ₃	CH ₃	H
1185	0	H	X	CF ₃	H	CF ₃	CH ₃	COCH ₃
1186	1	X	H	H	OH	H	H	H
1187	1	X	H	H	OH	H	H	COCH ₃
1188	1	X	H	H	OH	H	CH ₃	H
1189	1	X	H	H	OH	H	CH ₃	COCH ₃
1190	1	X	H	H	F	H	H	H
1191	1	X	H	H	F	H	H	COCH ₃
1192	1	X	H	H	F	H	CH ₃	H
1193	1	X	H	H	F	H	CH ₃	COCH ₃
1194	1	X	H	H	CF ₃	H	H	H
1195	1	X	H	H	CF ₃	H	H	COCH ₃
1196	1	X	H	H	CF ₃	H	CH ₃	H
1197	1	X	H	H	CF ₃	H	CH ₃	COCH ₃
1198	1	X	H	OH	OH	H	H	H
1199	1	X	H	OH	OH	H	H	COCH ₃

EXAMPLE NO.	n	R ¹¹	R ¹¹⁴	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1200	1	X	H	OH	OH	H	CH ₃	H
1201	1	X	H	OH	OH	H	CH ₃	C(=O)CH ₃
1202	1	X	H	F	H	F	H	H
1203	1	X	H	F	H	F	H	C(=O)CH ₃
1204	1	X	H	F	H	F	CH ₃	H
1205	1	X	H	F	H	F	CH ₃	C(=O)CH ₃
1206	1	X	H	CF ₃	H	CF ₃	H	H
1207	1	X	H	CF ₃	H	CF ₃	H	C(=O)CH ₃
1208	1	X	H	CF ₃	H	CF ₃	CH ₃	H
1209	1	X	H	CF ₃	H	CF ₃	CH ₃	C(=O)CH ₃
1210	1	H	X	H	OH	H	H	H
1211	1	H	X	H	OH	H	H	C(=O)CH ₃
1212	1	H	X	H	OH	H	CH ₃	H
1213	1	H	X	H	OH	H	CH ₃	C(=O)CH ₃
1214	1	H	X	H	F	H	H	H
1215	1	H	X	H	F	H	H	C(=O)CH ₃
1216	1	H	X	H	F	H	CH ₃	H
1217	1	H	X	H	F	H	CH ₃	C(=O)CH ₃
1218	1	H	X	H	CF ₃	H	H	H
1219	1	H	X	H	CF ₃	H	H	C(=O)CH ₃
1220	1	H	X	H	CF ₃	H	CH ₃	H
1221	1	H	X	H	CF ₃	H	CH ₃	C(=O)CH ₃
1222	1	H	X	1H	OH	H	H	H
1223	1	H	X	1H	OH	H	H	C(=O)CH ₃

EXAMPLE NO.	n	R ¹¹	R ¹¹⁴	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1224	1	H	X	1H	OH	H	CH ₃	H
1225	1	H	X	1H	OH	H	CH ₃	COCH ₃
1226	1	H	X	F	H	F	H	H
1227	1	H	X	F	H	F	H	C0CH ₃
1228	1	H	X	F	H	F	CH ₃	H
1229	1	H	X	F	H	F	CH ₃	COCH ₃
1230	1	H	X	CF ₃	H	CF ₃	H	H
1231	1	H	X	CF ₃	H	CF ₃	H	COCH ₃
1232	1	H	X	CF ₃	H	CF ₃	CH ₃	H
1233	1	H	X	CF ₃	H	CF ₃	CH ₃	COCH ₃
1234	2	X	H	H	OH	H	H	H
1235	2	X	H	H	OH	H	H	COCH ₃
1236	2	X	H	H	OH	H	CH ₃	H
1237	2	X	H	H	OH	H	CH ₃	COCH ₃
1238	2	X	H	H	F	H	H	H
1239	2	X	H	H	F	H	H	COCH ₃
1240	2	X	H	H	F	H	CH ₃	H
1241	2	X	H	H	F	H	CH ₃	COCH ₃
1242	2	X	H	H	CF ₃	H	H	H
1243	2	X	H	H	CF ₃	H	H	COCH ₃
1244	2	X	H	H	CF ₃	H	CH ₃	H
1245	2	X	H	H	CF ₃	H	CH ₃	COCH ₃
1246	2	X	H	OH	OH	H	H	H
1247	2	X	H	OH	OH	H	H	COCH ₃

EXAMPLE NO.	n	R ¹¹	R ¹¹⁴	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1248	2	X	H	OH	OH	H	CH ₃	H
1249	2	X	H	OH	OH	H	CH ₃	COCH ₃
1250	2	X	H	F	H	F	H	H
1251	2	X	H	F	H	F	H	COCH ₃
1252	2	X	H	F	H	F	CH ₃	H
1253	2	X	H	F	H	F	CH ₃	COCH ₃
1254	2	X	H	CF ₃	H	CF ₃	H	H
1255	2	X	H	CF ₃	H	CF ₃	H	COCH ₃
1256	2	X	H	CF ₃	H	CF ₃	CH ₃	H
1257	2	X	H	CF ₃	H	CF ₃	CH ₃	COCH ₃
1258	2	H	X	H	OH	H	H	H
1259	2	H	X	H	OH	H	H	COCH ₃
1260	2	H	X	H	OH	H	CH ₃	H
1261	2	H	X	H	OH	H	CH ₃	COCH ₃
1262	2	H	X	H	F	H	H	H
1263	2	H	X	H	F	H	H	COCH ₃
1264	2	H	X	H	F	H	CH ₃	H
1265	2	H	X	H	F	H	CH ₃	COCH ₃
1266	2	H	X	H	CF ₃	H	H	H
1267	2	H	X	H	CF ₃	H	H	COCH ₃
1268	2	H	X	H	CF ₃	H	CH ₃	H
1269	2	H	X	H	CF ₃	H	CH ₃	COCH ₃
1270	2	H	X	OH	OH	H	H	H
1271	2	H	X	OH	OH	H	H	COCH ₃

EXAMPLE NO.	n	R ¹¹	R ¹¹⁴	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1272	2	H	X	OH	OH	H	CH ₃	H
1273	2	H	X	OH	OH	H	CH ₃	COCH ₃
1274	2	H	X	F	H	F	H	H
1275	2	H	X	F	H	F	H	COCH ₃
1276	2	H	X	F	H	F	CH ₃	H
1277	2	H	X	F	H	F	CH ₃	COCH ₃
1278	2	H	X	CF ₃	H	CF ₃	H	H
1279	2	H	X	CF ₃	H	CF ₃	H	COCH ₃
1280	2	H	X	CF ₃	H	CF ₃	CH ₃	H
1281	2	H	X	CF ₃	H	CF ₃	CH ₃	COCH ₃
1282	3	X	H	H	OH	H	H	H
1283	3	X	H	H	OH	H	H	COCH ₃
1284	3	X	H	H	OH	H	CH ₃	H
1285	3	X	H	H	OH	H	CH ₃	COCH ₃
1286	3	X	H	H	F	H	H	H
1287	3	X	H	H	F	H	H	COCH ₃
1288	3	X	H	H	F	H	CH ₃	H
1289	3	X	H	H	F	H	CH ₃	COCH ₃
1290	3	X	H	H	CF ₃	H	H	H
1291	3	X	H	H	CF ₃	H	H	COCH ₃
1292	3	X	H	H	CF ₃	H	CH ₃	H
1293	3	X	H	H	CF ₃	H	CH ₃	COCH ₃
1294	3	X	H	OH	OH	H	H	H
1295	3	X	H	OH	OH	H	H	COCH ₃

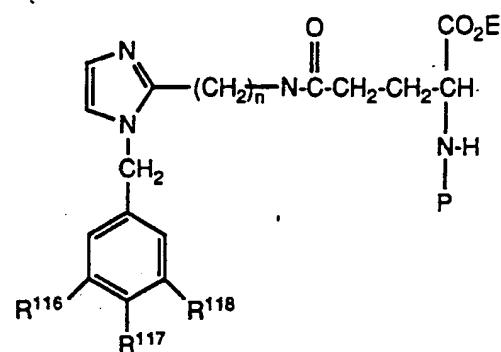
EXAMPLE NO.	n	R ¹¹	R ¹¹⁴	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1296	3	X	H	OH	OH	H	CH ₃	H
1297	3	X	H	OH	OH	H	CH ₃	COCH ₃
1298	3	X	H	F	H	F	H	H
1299	3	X	H	F	H	F	H	COCH ₃
1300	3	X	H	F	H	F	CH ₃	H
1301	3	X	H	F	H	F	CH ₃	COCH ₃
1302	3	X	H	CF ₃	H	CF ₃	H	H
1303	3	X	H	CF ₃	H	CF ₃	H	COCH ₃
1304	3	X	H	CF ₃	H	CF ₃	CH ₃	H
1305	3	X	H	CF ₃	H	CF ₃	CH ₃	COCH ₃
1306	3	H	X	H	OH	H	H	H
1307	3	H	X	H	OH	H	H	COCH ₃
1308	3	H	X	H	OH	H	CH ₃	H
1309	3	H	X	H	OH	H	CH ₃	COCH ₃
1310	3	H	X	H	F	H	H	H
1311	3	H	X	H	F	H	H	COCH ₃
1312	3	H	X	H	F	H	CH ₃	H
1313	3	H	X	H	F	H	CH ₃	COCH ₃
1314	3	H	X	H	CF ₃	H	H	H
1315	3	H	X	H	CF ₃	H	H	COCH ₃
1316	3	H	X	H	CF ₃	H	CH ₃	H
1317	3	H	X	H	CF ₃	H	CH ₃	COCH ₃
1318	3	H	X	OH	OH	H	H	H
1319	3	H	X	OH	OH	H	H	COCH ₃

EXAMPLE NO.	n	R ¹¹	R ¹¹⁴	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1320	3	H	X	OH	OH	H	CH ₃	H
1321	3	H	X	OH	OH	H	CH ₃	COCH ₃
1322	3	H	X	F	H	F	H	H
1323	3	H	X	F	H	F	H	COCH ₃
1324	3	H	X	F	H	F	CH ₃	H
1325	3	H	X	F	H	F	CH ₃	COCH ₃
1326	3	H	X	CF ₃	H	CF ₃	H	H
1327	3	H	X	CF ₃	H	CF ₃	H	COCH ₃
1328	3	H	X	CF ₃	H	CF ₃	CH ₃	H
1329	3	H	X	CF ₃	H	CF ₃	CH ₃	COCH ₃
1330	4	X	H	H	OH	H	H	H
1331	4	X	H	H	OH	H	H	COCH ₃
1332	4	X	H	H	OH	H	CH ₃	H
1333	4	X	H	H	OH	H	CH ₃	COCH ₃
1334	4	X	H	H	F	H	H	H
1335	4	X	H	H	F	H	H	COCH ₃
1336	4	X	H	H	F	H	CH ₃	H
1337	4	X	H	H	F	H	CH ₃	COCH ₃
1338	4	X	H	H	CF ₃	H	H	H
1339	4	X	H	H	CF ₃	H	H	COCH ₃
1340	4	X	H	H	CF ₃	H	CH ₃	H
1341	4	X	H	H	CF ₃	H	CH ₃	COCH ₃
1342	4	X	H	OH	OH	H	H	H
1343	4	X	H	OH	OH	H	H	COCH ₃

EXAMPLE NO.	n	R ¹¹	R ¹¹⁴	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1344	4	X	H	OH	OH	H	CH ₃	H
1345	4	X	H	OH	OH	H	CH ₃	COCH ₃
1346	4	X	H	F	H	F	H	H
1347	4	X	H	F	H	F	H	COCH ₃
1348	4	X	H	F	H	F	CH ₃	H
1349	4	X	H	F	H	F	CH ₃	COCH ₃
1350	4	X	H	CF ₃	H	CF ₃	H	H
1351	4	X	H	CF ₃	H	CF ₃	H	COCH ₃
1352	4	X	H	CF ₃	H	CF ₃	CH ₃	H
1353	4	X	H	CF ₃	H	CF ₃	CH ₃	COCH ₃
1354	4	H	X	H	OH	H	H	H
1355	4	H	X	H	OH	H	H	COCH ₃
1356	4	H	X	H	OH	H	CH ₃	H
1357	4	H	X	H	OH	H	CH ₃	COCH ₃
1358	4	H	X	H	F	H	H	H
1359	4	H	X	H	F	H	H	COCH ₃
1360	4	H	X	H	F	H	CH ₃	H
1361	4	H	X	H	F	H	CH ₃	COCH ₃
1362	4	H	X	H	CF ₃	H	H	H
1363	4	H	X	H	CF ₃	H	H	COCH ₃
1364	4	H	X	H	CF ₃	H	CH ₃	H
1365	4	H	X	H	CF ₃	H	CH ₃	COCH ₃
1366	4	H	X	OH	OH	H	H	H
1367	4	H	X	OH	OH	H	H	COCH ₃

EXAMPLE NO.	n	R ¹¹	R ¹¹⁴	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1368	4	H	X	OH	OH	H	CH ₃	H
1369	4	H	X	OH	OH	H	CH ₃	COCH ₃
1370	4	H	X	F	H	F	H	H
1371	4	H	X	F	H	F	H	COCH ₃
1372	4	H	X	F	H	F	CH ₃	H
1373	4	H	X	F	H	F	CH ₃	COCH ₃
1374	4	H	X	CF ₃	H	CF ₃	H	H
1375	4	H	X	CF ₃	H	CF ₃	H	COCH ₃
1376	4	H	X	CF ₃	H	CF ₃	CH ₃	H
1377	4	H	X	CF ₃	H	CF ₃	CH ₃	COCH ₃

The following Examples #1378-#1497 of Table XVI are highly preferred conjugates composed of dopamine- β -hydroxylase inhibitor compounds and glutamic acid derivatives. These dopamine- β -hydroxylase inhibitors utilized to make these conjugates are embraced by generic Formula XVIII, above.

TABLE XVI

EXAMPLE NO.	n	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1378	0	H	OH	H	H	H
1379	0	H	OH	H	H	COCH ₃
1380	0	H	OH	H	CH ₃	H
1381	0	H	OH	H	CH ₃	COCH ₃
1382	0	H	F	H	H	H
1383	0	H	F	H	H	COCH ₃
1384	0	H	F	H	CH ₃	H
1385	0	H	F	H	CH ₃	COCH ₃
1386	0	H	CF ₃	H	H	H
1387	0	H	CF ₃	H	H	COCH ₃
1388	0	H	CF ₃	H	CH ₃	H

EXAMPLE NO.	n	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1389	0	H	CF ₃	H	CH ₃	COCH ₃
1390	0	OH	OH	H	H	H
1391	0	OH	OH	H	H	COCH ₃
1392	0	OH	OH	H	CH ₃	H
1393	0	OH	OH	H	CH ₃	COCH ₃
1394	0	F	H	F	H	H
1395	0	F	H	F	H	COCH ₃
1396	0	F	H	F	CH ₃	H
1397	0	F	H	F	CH ₃	COCH ₃
1398	0	CF ₃	H	CF ₃	H	H
1399	0	CF ₃	H	CF ₃	H	COCH ₃
1400	0	CF ₃	H	CF ₃	CH ₃	H
1401	0	CF ₃	H	CF ₃	CH ₃	COCH ₃
1402	1	H	OH	H	H	H
1403	1	H	OH	H	H	COCH ₃
1404	1	H	OH	H	CH ₃	H

EXAMPLE NO.	n	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1405	1	H	OH	H	CH ₃	COCH ₃
1406	1	H	F	H	H	H
1407	1	H	F	H	H	COCH ₃
1408	1	H	F	H	CH ₃	H
1409	1	H	F	H	CH ₃	COCH ₃
1410	1	H	CF ₃	H	H	H
1411	1	H	CF ₃	H	H	COCH ₃
1412	1	H	CF ₃	H	CH ₃	H
1413	1	H	CF ₃	H	CH ₃	COCH ₃
1414	1	OH	OH	H	H	H
1415	1	OH	OH	H	H	COCH ₃
1416	1	OH	OH	H	CH ₃	H
1417	1	OH	OH	H	CH ₃	COCH ₃
1418	1	F	H	F	H	H
1419	1	F	H	F	H	COCH ₃
1420	1	F	H	F	CH ₃	H

EXAMPLE NO.	n	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1421	1	F	H	F	CH ₃	COCH ₃
1422	1	CF ₃	H	CF ₃	H	H
1423	1	CF ₃	H	CF ₃	H	COCH ₃
1424	1	CF ₃	H	CF ₃	CH ₃	H
1425	1	CF ₃	H	CF ₃	CH ₃	COCH ₃
1426	2	H	OH	H	H	H
1427	2	H	OH	H	H	COCH ₃
1428	2	H	OH	H	CH ₃	H
1429	2	H	OH	H	CH ₃	COCH ₃
1430	2	H	F	H	H	H
1431	2	H	F	H	H	COCH ₃
1432	2	H	F	H	CH ₃	H
1433	2	H	F	H	CH ₃	COCH ₃
1434	2	H	CF ₃	H	H	H
1435	2	H	CF ₃	H	H	COCH ₃
1436	2	H	CF ₃	H	CH ₃	H

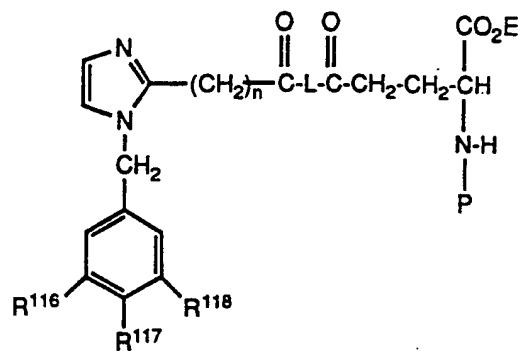
EXAMPLE NO.	n	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1437	2	H	CF ₃	H	CH ₃	COCH ₃
1438	2	OH	OH	H	H	H
1439	2	OH	OH	H	H	COCH ₃
1440	2	OH	OH	H	CH ₃	H
1441	2	OH	OH	H	CH ₃	COCH ₃
1442	2	F	H	F	H	H
1443	2	F	H	F	H	COCH ₃
1444	2	F	H	F	CH ₃	H
1445	2	F	H	F	CH ₃	COCH ₃
1446	2	CF ₃	H	CF ₃	H	H
1447	2	CF ₃	H	CF ₃	H	COCH ₃
1448	2	CF ₃	H	CF ₃	CH ₃	H
1449	2	CF ₃	H	CF ₃	CH ₃	COCH ₃
1450	3	H	OH	H	H	H
1451	3	H	OH	H	H	COCH ₃
1452	3	H	OH	H	CH ₃	H

EXAMPLE NO.	n	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1453	3	H	OH	H	CH ₃	COCH ₃
1454	3	H	F	H	H	H
1455	3	H	F	H	H	COCH ₃
1456	3	H	F	H	CH ₃	H
1457	3	H	F	H	CH ₃	COCH ₃
1458	3	H	CF ₃	H	H	H
1459	3	H	CF ₃	H	H	COCH ₃
1460	3	H	CF ₃	H	CH ₃	H
1461	3	H	CF ₃	H	CH ₃	COCH ₃
1462	3	OH	OH	H	H	H
1463	3	OH	OH	H	H	COCH ₃
1464	3	OH	OH	H	CH ₃	H
1465	3	OH	OH	H	CH ₃	COCH ₃
1466	3	F	H	F	H	H
1467	3	F	H	F	H	COCH ₃
1468	3	F	H	F	CH ₃	H

EXAMPLE NO.	n	R116	R117	R118	E	P
1469	3	F	H	F	CH ₃	COCH ₃
1470	3	CF ₃	H	CF ₃	H	H
1471	3	CF ₃	H	CF ₃	H	COCH ₃
1472	3	CF ₃	H	CF ₃	CH ₃	H
1473	3	CF ₃	H	CF ₃	CH ₃	COCH ₃
1474	4	H	OH	H	H	H
1475	4	H	OH	H	H	COCH ₃
1476	4	H	OH	H	CH ₃	H
1477	4	H	OH	H	CH ₃	COCH ₃
1478	4	H	F	H	H	H
1479	4	H	F	H	H	COCH ₃
1480	4	H	F	H	CH ₃	H
1481	4	H	F	H	CH ₃	COCH ₃
1482	4	H	CF ₃	H	H	H
1483	4	H	CF ₃	H	H	COCH ₃
1484	4	H	CF ₃	H	CH ₃	H

EXAMPLE NO.	n	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1485	4	H	CF ₃	H	CH ₃	COCH ₃
1486	4	OH	OH	H	H	H
1487	4	OH	OH	H	H	COCH ₃
1488	4	OH	OH	H	CH ₃	H
1489	4	OH	OH	H	CH ₃	COCH ₃
1490	4	F	H	F	H	H
1491	4	F	H	F	H	COCH ₃
1492	4	F	H	F	CH ₃	H
1493	4	F	H	F	CH ₃	COCH ₃
1494	4	CF ₃	H	CF ₃	H	H
1495	4	CF ₃	H	CF ₃	H	COCH ₃
1496	4	CF ₃	H	CF ₃	CH ₃	H
1497	4	CF ₃	H	CF ₃	CH ₃	COCH ₃

The following Examples #1498-#1857 of Table XVII are highly preferred conjugates composed of dopamine- β -hydroxylase inhibitor compounds and glutamic acid derivatives. These dopamine- β -hydroxylase inhibitors utilized to make these conjugates are embraced by generic Formula XVIII, above.

TABLE XVII

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1498	0	NHNH	H	OH	H	H	H
1499	0	NHNH	H	OH	H	H	COCH ₃
1500	0	NHNH	H	OH	H	CH ₃	H
1501	0	NHNH	H	OH	H	CH ₃	COCH ₃
1502	0	NHNH	H	F	H	H	H
1503	0	NHNH	H	F	H	H	COCH ₃
1504	0	NHNH	H	F	H	CH ₃	H
1505	0	NHNH	H	F	H	CH ₃	COCH ₃
1506	0	NHNH	H	CF ₃	H	H	H
1507	0	NHNH	H	CF ₃	H	H	COCH ₃
1508	0	NHNH	H	CF ₃	H	CH ₃	H

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1509	0	NHNH	H	CF ₃	H	CH ₃	COCH ₃
1510	0	NHNH	OH	OH	H	H	H
1511	0	NHNH	OH	OH	H	H	COCH ₃
1512	0	NHNH	OH	OH	H	CH ₃	H
1513	0	NHNH	OH	OH	H	CH ₃	COCH ₃
1514	0	NHNH	F	H	F	H	H
1515	0	NHNH	F	H	F	H	COCH ₃
1516	0	NHNH	F	H	F	CH ₃	H
1517	0	NHNH	F	H	F	CH ₃	COCH ₃
1518	0	NHNH	CF ₃	H	CF ₃	H	H
1519	0	NHNH	CF ₃	H	CF ₃	H	COCH ₃
1520	0	NHNH	CF ₃	H	CF ₃	CH ₃	H
1521	0	NHNH	CF ₃	H	CF ₃	CH ₃	COCH ₃
1522	0	NHCH ₂ CH ₂ NH	H	OH	H	H	H
1523	0	NHCH ₂ CH ₂ NH	H	OH	H	H	COCH ₃
1524	0	NHCH ₂ CH ₂ NH	H	OH	H	CH ₃	H

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1525	0	NHCH ₂ CH ₂ NH	H	OH	H	CH ₃	COCH ₃
1526	0	NHCH ₂ CH ₂ NH	H	F	H	H	H
1527	0	NHCH ₂ CH ₂ NH	H	F	H	H	COCH ₃
1528	0	NHCH ₂ CH ₂ NH	H	F	H	CH ₃	H
1529	0	NHCH ₂ CH ₂ NH	H	F	H	CH ₃	COCH ₃
1530	0	NHCH ₂ CH ₂ NH	H	CF ₃	H	H	H
1531	0	NHCH ₂ CH ₂ NH	H	CF ₃	H	H	COCH ₃
1532	0	NHCH ₂ CH ₂ NH	H	CF ₃	H	CH ₃	H
1533	0	NHCH ₂ CH ₂ NH	H	CF ₃	H	CH ₃	COCH ₃
1534	0	NHCH ₂ CH ₂ NH	OH	OH	H	H	H
1535	0	NHCH ₂ CH ₂ NH	OH	OH	H	H	COCH ₃
1536	0	NHCH ₂ CH ₂ NH	OH	OH	H	CH ₃	H
1537	0	NHCH ₂ CH ₂ NH	OH	OH	H	CH ₃	COCH ₃
1538	0	NHCH ₂ CH ₂ NH	F	H	F	H	H
1539	0	NHCH ₂ CH ₂ NH	F	H	F	H	COCH ₃
1540	0	NHCH ₂ CH ₂ NH	F	H	F	CH ₃	H

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1541	0	NHCH ₂ CH ₂ NH	F	H	F	CH ₃	COCH ₃
1542	0	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	H	H
1543	0	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	H	COCH ₃
1544	0	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	CH ₃	H
1545	0	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	CH ₃	COCH ₃
1546	0	piperazinyl	H	OH	H	H	H
1547	0	piperazinyl	H	OH	H	H	COCH ₃
1548	0	piperazinyl	H	OH	H	CH ₃	H
1549	0	piperazinyl	H	OH	H	CH ₃	COCH ₃
1550	0	piperazinyl	H	F	H	H	H
1551	0	piperazinyl	H	F	H	H	COCH ₃
1552	0	piperazinyl	H	F	H	CH ₃	H
1553	0	piperazinyl	H	F	H	CH ₃	COCH ₃
1554	0	piperazinyl	H	CF ₃	H	H	H
1555	0	piperazinyl	H	CF ₃	H	H	COCH ₃
1556	0	piperazinyl	H	CF ₃	H	CH ₃	H

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1557	0	piperazinyl	H	CF ₃	H	CH ₃	COCH ₃
1558	0	piperazinyl	OH	OH	H	H	H
1559	0	piperazinyl	OH	OH	H	H	COCH ₃
1560	0	piperazinyl	OH	OH	H	CH ₃	H
1561	0	piperazinyl	OH	OH	H	CH ₃	COCH ₃
1562	0	piperazinyl	F	H	F	H	H
1563	0	piperazinyl	F	H	F	H	COCH ₃
1564	0	piperazinyl	F	H	F	CH ₃	H
1565	0	piperazinyl	F	H	F	CH ₃	COCH ₃
1566	0	piperazinyl	CF ₃	H	CF ₃	H	H
1567	0	piperazinyl	CF ₃	H	CF ₃	H	COCH ₃
1568	0	piperazinyl	CF ₃	H	CF ₃	CH ₃	H
1569	0	piperazinyl	CF ₃	H	CF ₃	CH ₃	COCH ₃
1570	1	NHNH	H	OH	H	H	H
1571	1	NHNH	H	OH	H	H	COCH ₃
1572	1	NHNH	H	OH	H	CH ₃	H

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1573	1	NHNH	H	OH	H	CH ₃	COCH ₃
1574	1	NHNH	H	F	H	H	H
1575	1	NHNH	H	F	H	H	COCH ₃
1576	1	NHNH	H	F	H	CH ₃	H
1577	1	NHNH	H	F	H	CH ₃	COCH ₃
1578	1	NHNH	H	CF ₃	H	H	H
1579	1	NHNH	H	CF ₃	H	H	COCH ₃
1580	1	NHNH	H	CF ₃	H	CH ₃	H
1581	1	NHNH	H	CF ₃	H	CH ₃	COCH ₃
1582	1	NHNH	OH	OH	H	H	H
1583	1	NHNH	OH	OH	H	H	COCH ₃
1584	1	NHNH	OH	OH	H	CH ₃	H
1585	1	NHNH	OH	OH	H	CH ₃	COCH ₃
1586	1	NHNH	F	H	F	H	H
1587	1	NHNH	F	H	F	H	COCH ₃
1588	1	NHNH	F	H	F	CH ₃	H

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1589	1	NHNH	F	H	F	CH ₃	COCH ₃
1590	1	NHNH	CF ₃	H	CF ₃	H	H
1591	1	NHNH	CF ₃	H	CF ₃	H	COCH ₃
1592	1	NHNH	CF ₃	H	CF ₃	CH ₃	H
1593	1	NHNH	CF ₃	H	CF ₃	CH ₃	COCH ₃
1594	1	NHCH ₂ CH ₂ NH	H	OH	H	H	H
1595	1	NHCH ₂ CH ₂ NH	H	OH	H	H	COCH ₃
1596	1	NHCH ₂ CH ₂ NH	H	OH	H	CH ₃	H
1597	1	NHCH ₂ CH ₂ NH	H	OH	H	CH ₃	COCH ₃
1598	1	NHCH ₂ CH ₂ NH	H	F	H	H	H
1599	1	NHCH ₂ CH ₂ NH	H	F	H	H	COCH ₃
1600	1	NHCH ₂ CH ₂ NH	H	F	H	CH ₃	H
1601	1	NHCH ₂ CH ₂ NH	H	F	H	CH ₃	COCH ₃
1602	1	NHCH ₂ CH ₂ NH	H	CF ₃	H	H	H
1603	1	NHCH ₂ CH ₂ NH	H	CF ₃	H	H	COCH ₃
1604	1	NHCH ₂ CH ₂ NH	H	CF ₃	H	CH ₃	H

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1605	1	NHCH ₂ CH ₂ NH	H	CF ₃	H	CH ₃	COCH ₃
1606	1	NHCH ₂ CH ₂ NH	OH	OH	H	H	H
1607	1	NHCH ₂ CH ₂ NH	OH	OH	H	H	COCH ₃
1608	1	NHCH ₂ CH ₂ NH	OH	OH	H	CH ₃	H
1609	1	NHCH ₂ CH ₂ NH	OH	OH	H	CH ₃	COCH ₃
1610	1	NHCH ₂ CH ₂ NH	F	H	F	H	H
1611	1	NHCH ₂ CH ₂ NH	F	H	F	H	COCH ₃
1612	1	NHCH ₂ CH ₂ NH	F	H	F	CH ₃	H
1613	1	NHCH ₂ CH ₂ NH	F	H	F	CH ₃	COCH ₃
1614	1	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	H	H
1615	1	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	H	COCH ₃
1616	1	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	CH ₃	H
1617	1	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	CH ₃	COCH ₃
1618	1	piperazinyl	H	OH	H	H	H
1619	1	piperazinyl	H	OH	H	H	COCH ₃
1620	1	piperazinyl	H	OH	H	CH ₃	H

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1621	1	piperazinyl	H	OH	H	CH ₃	COCH ₃
1622	1	piperazinyl	H	F	H	H	H
1623	1	piperazinyl	H	F	H	H	COCH ₃
1624	1	piperazinyl	H	F	H	CH ₃	H
1625	1	piperazinyl	H	F	H	CH ₃	COCH ₃
1626	1	piperazinyl	H	CF ₃	H	H	H
1627	1	piperazinyl	H	CF ₃	H	H	COCH ₃
1628	1	piperazinyl	H	CF ₃	H	CH ₃	H
1629	1	piperazinyl	H	CF ₃	H	CH ₃	COCH ₃
1630	1	piperazinyl	OH	OH	H	H	H
1631	1	piperazinyl	OH	. OH	H	H	COCH ₃
1632	1	piperazinyl	OH	OH	H	CH ₃	H
1633	1	piperazinyl	OH	OH	H	CH ₃	COCH ₃
1634	1	piperazinyl	F	H	F	H	H
1635	1	piperazinyl	F	H	F	H	COCH ₃
1636	1	piperazinyl	F	H	F	CH ₃	H
1637	1	piperazinyl	F	H	F	CH ₃	COCH ₃

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1638	1	piperazinyl	CF ₃	H	CF ₃	H	H
1639	1	piperazinyl	CF ₃	H	CF ₃	H	COCH ₃
1640	1	piperazinyl	CF ₃	H	CF ₃	CH ₃	H
1641	1	piperazinyl	CF ₃	H	CF ₃	CH ₃	COCH ₃
1642	2	NHNH	H	OH	H	H	H
1643	2	NHNH	H	OH	H	H	COCH ₃
1644	2	NHNH	H	OH	H	CH ₃	H
1645	2	NHNH	H	OH	H	CH ₃	COCH ₃
1646	2	NHNH	H	F	H	H	H
1647	2	NHNH	H	F	H	H	COCH ₃
1648	2	NHNH	H	F	H	CH ₃	H
1649	2	NHNH	H	F	H	CH ₃	COCH ₃
1650	2	NHNH	H	CF ₃	H	H	H
1651	2	NHNH	H	CF ₃	H	H	COCH ₃
1652	2	NHNH	H	CF ₃	H	CH ₃	H
1653	2	NHNH	H	CF ₃	H	CH ₃	COCH ₃

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
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1654	2	NHNH	OH	OH	H	H	H
1655	2	NHNH	OH	OH	H	H	COCH ₃
1656	2	NHNH	OH	OH	H	CH ₃	H
1657	2	NHNH	OH	OH	H	CH ₃	COCH ₃
1658	2	NHNH	F	H	F	H	H
1659	2	NHNH	F	H	F	H	COCH ₃
1660	2	NHNH	F	H	F	CH ₃	H
1661	2	NHNH	F	H	F	CH ₃	COCH ₃
1662	2	NHNH	CF ₃	H	CF ₃	H	H
1663	2	NHNH	CF ₃	H	CF ₃	H	COCH ₃
1664	2	NHNH	CF ₃	H	CF ₃	CH ₃	H
1665	2	NHNH	CF ₃	H	CF ₃	CH ₃	COCH ₃
1666	2	NHCH ₂ CH ₂ NH	H	OH	H	H	H
1667	2	NHCH ₂ CH ₂ NH	H	OH	H	H	COCH ₃
1668	2	NHCH ₂ CH ₂ NH	H	OH	H	CH ₃	H
1669	2	NHCH ₂ CH ₂ NH	H	OH	H	CH ₃	COCH ₃

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1670	2	NHCH ₂ CH ₂ NH	H	F	H	H	H
1671	2	NHCH ₂ CH ₂ NH	H	F	H	H	COCH ₃
1672	2	NHCH ₂ CH ₂ NH	H	F	H	CH ₃	H
1673	2	NHCH ₂ CH ₂ NH	H	F	H	CH ₃	COCH ₃
1674	2	NHCH ₂ CH ₂ NH	H	CF ₃	H	H	H
1675	2	NHCH ₂ CH ₂ NH	H	CF ₃	H	H	COCH ₃
1676	2	NHCH ₂ CH ₂ NH	H	CF ₃	H	CH ₃	H
1677	2	NHCH ₂ CH ₂ NH	H	CF ₃	H	CH ₃	COCH ₃
1678	2	NHCH ₂ CH ₂ NH	OH	OH	H	H	H
1679	2	NHCH ₂ CH ₂ NH	OH	OH	H	H	COCH ₃
1680	2	NHCH ₂ CH ₂ NH	OH	OH	H	CH ₃	H
1681	2	NHCH ₂ CH ₂ NH	OH	OH	H	CH ₃	COCH ₃
1682	2	NHCH ₂ CH ₂ NH	F	H	F	H	H
1683	2	NHCH ₂ CH ₂ NH	F	H	F	H	COCH ₃
1684	2	NHCH ₂ CH ₂ NH	F	H	F	CH ₃	H
1685	2	NHCH ₂ CH ₂ NH	F	H	F	CH ₃	COCH ₃

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
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1686	2	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	H	H
1687	2	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	H	COCH ₃
1688	2	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	CH ₃	H
1689	2	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	CH ₃	COCH ₃
1690	2	piperazinyl	H	OH	H	H	H
1691	2	piperazinyl	H	OH	H	H	COCH ₃
1692	2	piperazinyl	H	OH	H	CH ₃	H
1693	2	piperazinyl	H	OH	H	CH ₃	COCH ₃
1694	2	piperazinyl	H	F	H	H	H
1695	2	piperazinyl	H	F	H	H	COCH ₃
1696	2	piperazinyl	H	F	H	CH ₃	H
1697	2	piperazinyl	H	F	H	CH ₃	COCH ₃
1698	2	piperazinyl	H	CF ₃	H	H	H
1699	2	piperazinyl	H	CF ₃	H	H	COCH ₃
1700	2	piperazinyl	H	CF ₃	H	CH ₃	H
1701	2	piperazinyl	H	CF ₃	H	CH ₃	COCH ₃

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
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1702	2	piperazinyl	OH	OH	H	H	H
1703	2	piperazinyl	OH	OH	H	H	COCH ₃
1704	2	piperazinyl	OH	OH	H	CH ₃	H
1705	2	piperazinyl	OH	OH	H	CH ₃	COCH ₃
1706	2	piperazinyl	F	H	F	H	H
1707	2	piperazinyl	F	H	F	H	COCH ₃
1708	2	piperazinyl	F	H	F	CH ₃	H
1709	2	piperazinyl	F	H	F	CH ₃	COCH ₃
1710	2	piperazinyl	CF ₃	H	CF ₃	H	H
1711	2	piperazinyl	CF ₃	H	CF ₃	H	COCH ₃
1712	2	piperazinyl	CF ₃	H	CF ₃	CH ₃	H
1713	2	piperazinyl	CF ₃	H	CF ₃	CH ₃	COCH ₃
1714	3	NHNH	H	OH	H	H	H
1715	3	NHNH	H	OH	H	H	COCH ₃
1716	3	NHNH	H	OH	H	CH ₃	H
1717	3	NHNH	H	OH	H	CH ₃	COCH ₃

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1718	3	NHNH	H	F	H	H	H
1719	3	NHNH	H	F	H	H	COCH ₃
1720	3	NHNH	H	F	H	CH ₃	H
1721	3	NHNH	H	F	H	CH ₃	COCH ₃
1722	3	NHNH	H	CF ₃	H	H	H
1723	3	NHNH	H	CF ₃	H	H	COCH ₃
1724	3	NHNH	H	CF ₃	H	CH ₃	H
1725	3	NHNH	H	CF ₃	H	CH ₃	COCH ₃
1726	3	NHNH	OH	OH	H	H	H
1727	3	NHNH	OH	OH	H	H	COCH ₃
1728	3	NHNH	OH	OH	H	CH ₃	H
1729	3	NHNH	OH	OH	H	CH ₃	COCH ₃
1730	3	NHNH	F	H	F	H	H
1731	3	NHNH	F	H	F	H	COCH ₃
1732	3	NHNH	F	H	F	CH ₃	H
1733	3	NHNH	F	H	F	CH ₃	COCH ₃

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1734	3	NHNH	CF ₃	H	CF ₃	H	H
1735	3	NHNH	CF ₃	H	CF ₃	H	COCH ₃
1736	3	NHNH	CF ₃	H	CF ₃	CH ₃	H
1737	3	NHNH	CF ₃	H	CF ₃	CH ₃	COCH ₃
1738	3	NHCH ₂ CH ₂ NH	H	OH	H	H	H
1739	3	NHCH ₂ CH ₂ NH	H	OH	H	H	COCH ₃
1740	3	NHCH ₂ CH ₂ NH	H	OH	H	CH ₃	H
1741	3	NHCH ₂ CH ₂ NH	H	OH	H	CH ₃	COCH ₃
1742	3	NHCH ₂ CH ₂ NH	H	F	H	H	H
1743	3	NHCH ₂ CH ₂ NH	H	F	H	H	COCH ₃
1744	3	NHCH ₂ CH ₂ NH	H	F	H	CH ₃	H
1745	3	NHCH ₂ CH ₂ NH	H	F	H	CH ₃	COCH ₃
1746	3	NHCH ₂ CH ₂ NH	H	CF ₃	H	H	H
1747	3	NHCH ₂ CH ₂ NH	H	CF ₃	H	H	COCH ₃
1748	3	NHCH ₂ CH ₂ NH	H	CF ₃	H	CH ₃	H
1749	3	NHCH ₂ CH ₂ NH	H	CF ₃	H	CH ₃	COCH ₃

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1750	3	NHCH ₂ CH ₂ NH	OH	OH	H	H	H
1751	3	NHCH ₂ CH ₂ NH	OH	OH	H	H	COCH ₃
1752	3	NHCH ₂ CH ₂ NH	OH	OH	H	CH ₃	H
1753	3	NHCH ₂ CH ₂ NH	OH	OH	H	CH ₃	COCH ₃
1754	3	NHCH ₂ CH ₂ NH	F	H	F	H	H
1755	3	NHCH ₂ CH ₂ NH	F	H	F	H	COCH ₃
1756	3	NHCH ₂ CH ₂ NH	F	H	F	CH ₃	H
1757	3	NHCH ₂ CH ₂ NH	F	H	F	CH ₃	COCH ₃
1758	3	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	H	H
1759	3	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	H	COCH ₃
1760	3	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	CH ₃	H
1761	3	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	CH ₃	COCH ₃
1762	3	piperazinyl	H	OH	H	H	H
1763	3	piperazinyl	H	OH	H	H	COCH ₃
1764	3	piperazinyl	H	OH	H	CH ₃	H
1765	3	piperazinyl	H	OH	H	CH ₃	COCH ₃

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1766	3	piperazinyl	H	F	H	H	H
1767	3	piperazinyl	H	F	H	H	COCH ₃
1768	3	piperazinyl	H	F	H	CH ₃	H
1769	3	piperazinyl	H	F	H	CH ₃	COCH ₃
1770	3	piperazinyl	H	CF ₃	H	H	H
1771	3	piperazinyl	H	CF ₃	H	H	COCH ₃
1772	3	piperazinyl	H	CF ₃	H	CH ₃	H
1773	3	piperazinyl	H	CF ₃	H	CH ₃	COCH ₃
1774	3	piperazinyl	OH	OH	H	H	H
1775	3	piperazinyl	OH	OH	H	H	COCH ₃
1776	3	piperazinyl	OH	OH	H	CH ₃	H
1777	3	piperazinyl	OH	OH	H	CH ₃	COCH ₃
1778	3	piperazinyl	F	H	F	H	H
1779	3	piperazinyl	F	H	F	H	COCH ₃
1780	3	piperazinyl	F	H	F	CH ₃	H
1781	3	piperazinyl	F	H	F	CH ₃	COCH ₃

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1782	3	piperazinyl	CF ₃	H	CF ₃	H	H
1783	3	piperazinyl	CF ₃	H	CF ₃	H	COCH ₃
1784	3	piperazinyl	CF ₃	H	CF ₃	CH ₃	H
1785	3	piperazinyl	CF ₃	H	CF ₃	CH ₃	COCH ₃
1786	4	NHNH	H	OH	H	H	H
1787	4	NHNH	H	OH	H	H	COCH ₃
1788	4	NHNH	H	OH	H	CH ₃	H
1789	4	NHNH	H	OH	H	CH ₃	COCH ₃
1790	4	NHNH	H	F	H	H	H
1791	4	NHNH	H	F	H	H	COCH ₃
1792	4	NHNH	H	F	H	CH ₃	H
1793	4	NHNH	H	F	H	CH ₃	COCH ₃
1794	4	NHNH	H	CF ₃	H	H	H
1795	4	NHNH	H	CF ₃	H	H	COCH ₃
1796	4	NHNH	H	CF ₃	H	CH ₃	H
1797	4	NHNH	H	CF ₃	H	CH ₃	COCH ₃

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1798	4	NHNH	OH	OH	H	H	H
1799	4	NHNH	OH	OH	H	H	COCH ₃
1800	4	NHNH	OH	OH	H	CH ₃	H
1801	4	NHNH	OH	OH	H	CH ₃	COCH ₃
1802	4	NHNH	F	H	F	H	H
1803	4	NHNH	F	H	F	H	COCH ₃
1804	4	NHNH	F	H	F	CH ₃	H
1805	4	NHNH	F	H	F	CH ₃	COCH ₃
1806	4	NHNH	CF ₃	H	CF ₃	H	H
1807	4	NHNH	CF ₃	H	CF ₃	H	COCH ₃
1808	4	NHNH	CF ₃	H	CF ₃	CH ₃	H
1809	4	NHNH	CF ₃	H	CF ₃	CH ₃	COCH ₃
1810	4	NHCH ₂ CH ₂ NH	H	OH	H	H	H
1811	4	NHCH ₂ CH ₂ NH	H	OH	H	H	COCH ₃
1812	4	NHCH ₂ CH ₂ NH	H	OH	H	CH ₃	H
1813	4	NHCH ₂ CH ₂ NH	H	OH	H	CH ₃	COCH ₃

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1814	4	NHCH ₂ CH ₂ NH	H	F	H	H	H
1815	4	NHCH ₂ CH ₂ NH	H	F	H	H	COCH ₃
1816	4	NHCH ₂ CH ₂ NH	H	F	H	CH ₃	H
1817	4	NHCH ₂ CH ₂ NH	H	F	H	CH ₃	COCH ₃
1818	4	NHCH ₂ CH ₂ NH	H	CF ₃	H	H	H
1819	4	NHCH ₂ CH ₂ NH	H	CF ₃	H	H	COCH ₃
1820	4	NHCH ₂ CH ₂ NH	H	CF ₃	H	CH ₃	H
1821	4	NHCH ₂ CH ₂ NH	H	CF ₃	H	CH ₃	COCH ₃
1822	4	NHCH ₂ CH ₂ NH	OH	OH	H	H	H
1823	4	NHCH ₂ CH ₂ NH	OH	OH	H	H	COCH ₃
1824	4	NHCH ₂ CH ₂ NH	OH	OH	H	CH ₃	H
1825	4	NHCH ₂ CH ₂ NH	OH	OH	H	CH ₃	COCH ₃
1826	4	NHCH ₂ CH ₂ NH	F	H	F	H	H
1827	4	NHCH ₂ CH ₂ NH	F	H	F	H	COCH ₃
1828	4	NHCH ₂ CH ₂ NH	F	H	F	CH ₃	H
1829	4	NHCH ₂ CH ₂ NH	F	H	F	CH ₃	COCH ₃

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1830	4	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	H	H
1831	4	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	H	COCH ₃
1832	4	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	CH ₃	H
1833	4	NHCH ₂ CH ₂ NH	CF ₃	H	CF ₃	CH ₃	COCH ₃
1834	4	piperazinyl	H	OH	H	H	H
1835	4	piperazinyl	H	OH	H	H	COCH ₃
1836	4	piperazinyl	H	OH	H	CH ₃	H
1837	4	piperazinyl	H	OH	H	CH ₃	COCH ₃
1838	4	piperazinyl	H	F	H	H	H
1839	4	piperazinyl	H	F	H	H	COCH ₃
1840	4	piperazinyl	H	F	H	CH ₃	H
1841	4	piperazinyl	H	F	H	CH ₃	COCH ₃
1842	4	piperazinyl	H	CF ₃	H	H	H
1843	4	piperazinyl	H	CF ₃	H	H	COCH ₃
1844	4	piperazinyl	H	CF ₃	H	CH ₃	H
1845	4	piperazinyl	H	CF ₃	H	CH ₃	COCH ₃

EXAMPLE NO.	n	L	R ¹¹⁶	R ¹¹⁷	R ¹¹⁸	E	P
1846	4	piperazinyl	OH	OH	H	H	H
1847	4	piperazinyl	OH	OH	H	H	COCH ₃
1848	4	piperazinyl	OH	OH	H	CH ₃	H
1849	4	piperazinyl	OH	OH	H	CH ₃	COCH ₃
1850	4	piperazinyl	F	H	F	H	H
1851	4	piperazinyl	F	H	F	H	COCH ₃
1852	4	piperazinyl	F	H	F	CH ₃	H
1853	4	piperazinyl	F	H	F	CH ₃	COCH ₃
1854	4	piperazinyl	CF ₃	H	CF ₃	H	H
1855	4	piperazinyl	CF ₃	H	CF ₃	H	COCH ₃
1856	4	piperazinyl	CF ₃	H	CF ₃	CH ₃	H
1857	4	piperazinyl	CF ₃	H	CF ₃	CH ₃	COCH ₃

BIOLOGICAL EVALUATION

- Conjugates of the invention were evaluated biologically by in vitro and in vivo assays to determine
5 the ability of the conjugates to selectively inhibit renal sympathetic nerve activity and lower blood pressure. Three classes of conjugates of the invention were evaluated for their ability to inhibit the enzymes of the catecholamine cascade selectively within the kidney. These inhibitor
10 conjugates variously inhibit tyrosine hydroxylase, dopa-decarboxylase and dopamine- β -hydroxylase in order to interfere ultimately with the synthesis of norepinephrine in the kidney.
- 15 Assays I and II evaluate in vivo the acute and chronic effects of Ex. #3 conjugate (a tyrosine hydroxylase inhibitor conjugated with N-acetyl- γ -glutamyl) in rats. Assay III evaluates the chronic effects of Ex. #464 conjugate (a dopa-decarboxylase inhibitor conjugated with
20 N-acetyl- γ -glutamyl) in rats.

Assay IV and V describes in vitro experiments performed to determine if the Ex. #859 conjugate was capable of being specifically metabolized by enzymes known
25 to be abundant in the kidney. In Assay IV, the Ex. #859 conjugate was incubated with either rat kidney homogenate or a solution containing purified kidney enzymes to characterize resulting metabolites. In Assay V, experiments were performed to determine the potency of the
30 Ex. #858 and Ex. #859 conjugates and potential metabolites as inhibitors of purified dopamine- β -hydroxylase.

Assays VI through IX describe in vivo experiments performed to characterize and compare the effects of fusaric acid and various conjugates of fusaric acid (Ex. #859, Ex.
35 #861 and Ex. #863) on spontaneously hypertensive rats (SHR) by

acute administration i.v. and i.d. and by chronic administration i.v. Assay X describes analysis of catecholamine levels in tissue from rats used in the chronic administration experiment of Assay VIII. Assays XI and XII 5 describe in vivo experiments in dogs to determine the renal and mean arterial pressure effects of fusaric acid and Ex. #859 conjugate.

Assay I: Acute In Vivo Effects of Ex. #3 Conjugate

10

Sprague-Dawley rats were anesthetized with inactin (100 mg/kg, i.p.) and catheters were implanted into a carotid artery for measurement of mean arterial pressure (Gould model 3800 chart recorder; Statham pressure 15 transducer model no. P23DB) and into a jugular vein for compound administrations (i.v.). In addition, a flow probe was implanted around the left renal artery for measurement of renal blood flow using Carolina Medical Electronics flow probes. Rats were allowed 60 min to stabilize before 10 minutes of control recordings of mean arterial pressure and renal blood flow were obtained. Control measurements were followed by intravenous injection of Ex. #3 conjugate and saline vehicle. As shown in Table XVIII and in Figs. 1 and 2, the Ex. #3 conjugate had no acute effects on mean 20 arterial pressure (MAP), but increased renal blood flow 25 (RBF).

TABLE XVIIIAcute In Vivo Effects of Ex. #3 Conjugate

5

Time After Injection (min)

	Zero	15	30	45	60
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10

Vehicle (0.5 ml 0.9% NaCl i.v.)

MAP (mm Hg)	78	76	75	80	82
RBF (ml/min)	4.9	4.5	4.2	4.6	4.7

15

Ex. #3 Conjugate (100 mg/kg i.v.)

MAP (mm Hg)	76 ± 5	77 ± 5	73 ± 4	70 ± 2	71 ± 6
RBF (ml/min)	4.8 ± 0.8	7.1 ± 0.1	6.2 ± 0.3	5.9 ± 0.1	5.9 ± 0.1

20

Assay II: Chronic In Vivo Effects of Ex. #3 Conjugate

The Ex. #3 conjugate and saline vehicle were infused continuously for four days in spontaneously hypertensive rats. Mean arterial pressure was measured (Gould Chart Recorder, model 3800; Statham P23Db pressure transducer) via an indwelling femoral artery catheter between 10:00 a.m. and 2:00 p.m. each day. The Ex. #3 conjugate was infused at 5 mg/hr and the saline vehicle was infused at 300 μ L/hr. via a jugular vein catheter with a Harvard infusion pump. Results are shown in Table XIX.

TABLE XIXChronic In Vivo Effects of Ex. #3 Conjugate

5

Time After Injection (days)

	Zero	1	2	3	4
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10

Vehicle (300 µL/hr)

MAP (mm Hg)	181 ± 8	172 ± 6	170 ± 7	174 ± 6	182 ± 3
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Ex. #3 Conjugate (5 mg/hr)

15

MAP (mm Hg)	164 ± 3	175 ± 5	174 ± 5	172 ± 2	N.A.
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Assay III: Chronic In Vivo Effects of Ex. #464 Conjugate

The Ex. #464 conjugate and saline vehicle were infused continuously for four days in spontaneously hypertensive rats. Mean arterial pressure was measured (Gould Chart Recorder, model 3800; Statham P23Db pressure transducer) via an indwelling femoral artery catheter between 10:00 a.m. and 2:00 p.m. each day. The Ex. #464 conjugate was infused at 10 mg/hr and the saline vehicle was infused at 300 µL/hr. As shown in Table XX and in Fig. 30 3, mean arterial pressure was lowered significantly over the four-day period.

TABLE XXChronic In Vivo Effects of Ex. #464 Conjugate

5

Time After Injection (days)

Zero 1 2 3 4

Vehicle (300 µL/hr)

10

MAP (mm Hg) 181±8 172±6 170±7 174±6 182±3

Ex. #464 Conjugate (10 mg/hr)

15

MAP (mm Hg) 179±6 169±5 161±4 163±5 159±8

20 Assay IV: In Vitro Evaluation of Enzyme Metabolism Effects of Ex. #859 Conjugate

A freshly excised rat kidney was homogenized in 10 ml cold buffer (100 mM Tris, 15mM glycylglycine, pH 7.4) 25 with a Polytron Tissue Homogenizer (Brinkmann). The resulting suspension, diluted with buffer, was incubated in the presence of the Ex. #859 conjugate at 37°C. At various times aliquots were removed, deproteinized with an equal volume of cold trichloroacetic acid (25%) and centrifuged. 30 The supernatant was injected onto a C-18 reverse-phase HPLC column and eluted isocratically with a mixture of acetonitrile and water (20:80 v/v) containing trifluoroacetic acid (0.05%). Eluted compounds were monitored by absorbance at 254 nm and compared to standards 35 run under identical conditions. In the assay using pure kidney enzyme homogenate,, the Ex. #859 conjugate was also

incubated under the same conditions as described except that 5 mg of gamma-glutamyl transpeptidase (Sigma, 23 units/mg) and 10 mg of acylase I (Sigma, 4800 units/mg) were added in place of the homogenate. Analysis by HPLC was 5 performed in a manner identical to that used for the kidney homogenate experiment. Following incubation of the Ex. #859 conjugate with kidney homogenate, there was a linear increase in the amount of fusaric acid liberated, as shown in Figure 4. No fusaric acid hydrazide or gamma- 10 glutamyl fusaric acid hydrazide was observed; nor was any metabolism observed in the buffer control incubations. These data (Table XXI, Figure 4) show that renal tissue is able to metabolize the Ex. #859 conjugate to fusaric acid, which then remains stable under these conditions. Data from 15 experiments using the purified enzymes show results similar to those seen for the kidney homogenate experiment, with only fusaric acid and the unreacted compound being present (see Table XXII, Figure 5).

TABLE XXI

5 Formation of Fusaric Acid From the Ex. #859 Conjugate Incubated with Kidney Homogenate

	Time (hrs.) :	0.00	0.17	1.25	17.00	41.00
10						
	Fusaric Acid (μg/ml) :	0.00	0.27	0.57	2.37	5.94

15

TABLE XXII

20 Formation of Fusaric Acid From Ex. #859 Conjugate Incubated with Purified Transpeptidase and Acylase

	Time (hrs.) :	3	24	72	96	120
25						
	Fusaric Acid (μg/ml) :	0.00	2.56	12.15	15.44	18.75
	@ pH 7.4					
30						
	Fusaric Acid (μg/ml) :	0.00	1.12	4.46	5.22	6.55
	@ pH 8.1					

Assay V: In Vitro Evaluation of DBH Inhibition by Ex. #859 Conjugate

In order to characterize the relative potency of
5 the Ex. #859 conjugate and its various potential
metabolites as inhibitors of dopamine beta-hydroxylase
(DBH; EC 1.14.17.1), the enzyme activity was determined *in*
vitro in the presence of these compounds. DBH, purified
from bovine adrenals (Sigma) was incubated at 37°C in
10 buffer containing 20 mM dopamine as substrate. The reaction
was stopped by addition of 0.5 M perchloric acid. The
precipitate was removed and the product of the enzyme
activity (norepinephrine), contained in the clear
supernatant, was analyzed by HPLC. The chromatographic
15 separation used a reversed phase C-18 column run
isocratically with 0.2 M ammonium acetate (pH 5.2) as the
mobile phase. The amount of norepinephrine produced by the
enzyme-substrate mixture was analyzed by measuring the peak
intensity (absorbance) at 280 nm for norepinephrine as it
20 was eluted at 4.5 minutes, using a photo-diode array
detector. The result of adding either fusaric acid or the
Ex. #859 conjugate to the incubate at various
concentrations is shown in Table XXIII and Figure 6. Above
25 concentrations of 1 uM, fusaric acid inhibits the enzyme,
while at concentrations up to 100 uM the Ex. #859 conjugate
has no appreciable activity (Table XXIII and Figure 6).
Fusaric acid and Ex. #859 and two more possible metabolites
(Ex #858 and fusaric acid hydrazide) were tested at 20 uM.
Only fusaric acid had significant inhibitory effects on
30 dopamine-β-hydroxylase activity (Table XXIV and Figure 7).

TABLE XXIII
DBH Inhibition by Fusaric Acid and the Ex. #859 Conjugate

Concentration (μM) :	0.01	0.10	0.50	1.00	5.00	10.00	50.00	100.00
<hr/>								
Norepinephrine Peak Intensity (Abs 280) in the presence of Fusaric Acid:	0.59	0.59	0.60	0.53	0.25	0.14	0.00	0.00
Norepinephrine Peak Intensity (Abs 280) in the presence of Ex. #859 Conjugate	0.51	0.52	0.61	0.53				

TABLE XXIVDBH Inhibition by Fusaric Acid, Ex. #859 Conjugate
and Various Potential Metabolites

Test	Ex.	Ex.	Fusaric Acid	Fusaric Acid
Compound (20 μ M):	#859	#858	Hydrazide	Acid
% Inhibition :	1.5	0.0	13.8	75.4

Assay VI: Acute In Vivo Effects of Ex. #859 and Ex. #863
Conjugates

Spontaneously hypertensive rats were anesthetized
with inactin (100 mg/kg, i.p.) and catheters were implanted
into a carotid artery for measurement of mean arterial
pressure (Gould model 3800 chart recorder; Statham pressure
transducer model no. P23DB) and into a jugular vein for
compound administrations (i.v. or i.d.). In addition, a flow
probe was implanted around the left renal artery for
measurement of renal blood flow using pulsed Doppler
flowmetry. Rats were allowed 60 min to stabilize before 10
minutes of control recordings of mean arterial pressure and
renal blood flow were obtained. Control measurements were
followed by intravenous injection of 50 mg/kg of fusaric acid
or the Ex. #859 conjugate. As shown in Figures 8 and 9 and
Table XXV, fusaric acid (a systemic dopamine- β -hydroxylase
inhibitor) decreased mean arterial pressure and increased
renal blood flow throughout the 60 minute post-injection
observation period. In sharp contrast, the Ex. #859 conjugate
had no acute effects on mean arterial pressure, but increased

renal blood flow to a greater degree than fusaric acid (Table XXV and Figures 8 and 9). Similar results were found when these compounds were administered through a catheter implanted into the duodenum (i.d.). The Ex. #859 conjugate had no effect on mean arterial pressure at a dose of 100 mg/kg (n=4) during a 60 minute observation period. Renal blood flow (n=4) was unchanged 15 minutes after injection of the Ex. #859 conjugate but increased from 1.1 KHz (control period) to 3.5 KHz at 30 minutes postinjection. Renal blood flow remained at this level for the following 30 minute observation period. These data indicate that the Ex. #859 conjugate is active and displays renal selectivity whether administered i.d. or i.v. Results for Ex. #863 conjugate were similar to Ex. #859 and are shown in Table XXVI: Ex. #863 had no effect on mean arterial pressure, but increased renal blood flow, indicating renal selectivity.

TABLE XXV

20 Acute Effects of Fusaric Acid and Ex. #859 conjugate on Blood Pressure and Renal Blood Flow

	<u>Time (min)</u>				
	Zero	15	30	45	60
<u>Fusaric Acid (50mg/kg i.v.)</u>					
MAP (mm Hg)	155	111	106	103	99
RBF (KHz)	2.5	3.1	3.2	3.4	3.9
<u>Ex. #859 Conjugate (50 mg/kg i.v.)</u>					
MAP (mm Hg)	156	163	164	157	159
RBF (KHz)	2.4	3.8	4.0	4.6	4.8

Table XXVIAcute Effects of Ex. #863 Conjugate

5

Time (min)

Zero 15 30 45 60

Ex. #863 (100 mg/kg i.v.)

10

MAP (mm Hg)	149 ± 14	N.A.	N.A.	N.A.	147 ± 14
RBF (KHz)	1.6 ± 0.2	N.A.	N.A.	N.A.	4.3 ± 0.3

15 N.A. = Not Available

20 Assay VII: Comparison of Fusaric Acid, Fusaric Acid Hydrazide
and Ex. #859 Conjugate on Arterial Pressure in Spontaneously
Hypertensive Rats (SHR)

25 Mean arterial pressure effects of fusaric acid hydrazide (100 mg/kg, i.v.), fusaric acid (100 mg/kg, i.v.) and Ex. #859 conjugate (250 mg/kg, i.v.) are shown in Table XXVII during a vehicle control period and 60 min post-injection of compound in anesthetized SHR. Rats were prepared as described above, minus the renal artery flow probe.

Table XXVII

<u>COMPOUND</u>	<u>ZERO</u>	<u>60 MIN</u>
Fusaric Acid (n=4)	164 ± 10 mmHg	110 ± 21 mmHg
Fusaric Acid Hydrazide (n=4)	159 ± 8 mmHg	104 ± 13 mmHg
Ex. #859 Conjugate (n=4)	151 ± 9 mmHg	146 ± 15 mmHg

The data show that the hypotensive effects of the fusaric acid hydrazide is similar to fusaric acid. The Ex. #859 conjugate had no effect on mean arterial pressure (Table XXV and Figure 8).

20 Assay VIII: Chronic In Vivo Effects of Ex. #859 Conjugate

The Ex. #859 conjugate and saline vehicle were infused continuously for 5 days in SHR. Mean arterial pressure was measured (Gould Chart Recorder, model 3800; Statham P23Db pressure transducer) via an indwelling femoral artery catheter between 10:00 a.m. and 2:00 p.m. each day. The Ex. #859 conjugate (5 mg/hr), fusaric acid (2.5 mg/hr), and saline (100 µl/hr) were infused via a jugular vein catheter with a Harvard infusion pump. Compared to the control vehicle fusaric acid and the Ex. #859 conjugate lowered mean arterial pressure similarly. Mean arterial pressure did not change in the saline vehicle group. Results are shown in Table XXVIII and Figure 10.

TABLE XXVIIIChronic Effects of Fusaric Acid and Ex. #859 Conjugate
on Blood Pressure

5

	<u>Time (days)</u>						
	Zero	1	2	3	4	5	
10							
	<u>Vehicle (25 µL/hr)</u>						
	MAP (mm Hg)	139±2	139±4	143±4	146±4	145±7	146±4
	(SE)						
15							
	<u>Fusaric Acid (2.5 mg/hr)</u>						
	MAP (mm Hg)	148±6	118±5	114±7	122±5	114±6	114±3
	(SE)						
20							
	<u>Ex. #859 Conjugate (5 mg/hr)</u>						
	MAP (mm Hg)	146±5	122±9	115±9	119±11	121±7	115±8
	(SE)						
25							

Assay IX: Chronic In Vivo Effects of Ex. #861 and Ex. #863 Conjugates

The conjugates of Ex. #861 and #863 and saline vehicle were infused continuously for 4 days in spontaneously hypertensive rats. Mean arterial pressure was measured (Gould Chart Recorder, model 3800; Statham P23Db pressure transducer) via an indwelling femoral artery catheter between 10:00 a.m. and 2:00 p.m. each day. The Ex. #861 and Ex. #863 conjugates were infused at 5 mg/hr and the saline vehicle was infused at 100 µl/hr via a jugular vein catheter with a Harvard infusion pump. Results are shown in Table XXIX. The Ex. #863 conjugate lowered mean arterial pressure as shown in Fig. 11. Mean arterial pressure did not change for the Ex. #861 conjugate and the saline vehicle group (Table XXIX). It is believed that at a higher dose of the Ex. #861 conjugate, blood pressure lowering effects would be observed.

TABLE XXIX

20

Chronic Effects of Ex. #861 and Ex. #863 Conjugates on Blood Pressure

		<u>Time (days)</u>				
25		Zero	1	2	3	4
	Vehicle	171±6	172±6	164±6	169±4	162±4
	Ex. #861	177±3	173±3	172±4	172±3	163±9
30	Ex. #863	177±5	152±6	146±7	142±7	154±7

Assay X: Catecholamine Analysis of Tissue from Rats
Treated with Ex. #859 Conjugate

In order to evaluate the renal selectivity of DBH inhibition by the Ex. #859 conjugate, the catecholamine levels of heart and kidneys, both of which have been shown to be highly sensitive to DBH inhibition [Racz, K. et al., *Europ. J. Pharmacol.*, 102, 1 (1985)], were measured following chronic infusion of the Ex. #859 conjugate, fusaric acid and saline vehicle in rats. Following 5 days of infusion, the kidney was exposed through a small flank incision, made in the anesthetized rat, and the renal artery and vein were ligated. Following this the kidney was rapidly excised distal to the ligation and frozen in liquid nitrogen. Similarly, the heart was excised and frozen subsequent to the removal of both kidneys. The frozen tissues were stored in closed containers at -80°C. Tissue samples were thawed on ice and their weight recorded prior to being placed in a flat bottom tube. The cold extraction solvent (2 ml/g tissue) was then added and the sample was homogenized with a Polytron. Extraction Solvent: 0.1 M perchloric acid (3 ml of 70% PCA to 500 ml); 0.4 mM Na metabisulphite (38 mg/500 ml). The volume was then measured and 0.05 ml of a 1 μM/L solution of dihydroxybenzylamine (DHBA) in extraction solvent was added for every 0.95 ml of homogenate to yield a 50 nM/L internal standard concentration. The homogenate was then mixed and centrifuged at 4°C, 3000 rpm for 35 minutes. A 2 ml aliquot of the supernatant was then neutralized by adding 0.5 ml of 2 M Tris, pH 8.8 and mixing. The sample was then placed on an alumina column (40 mg, Spe-ed CAT cartridge; Applied Separations; Bethlehem, PA) and the catecholamines were bound, washed and eluted using a vacuum manifold system (Adsorbex SPU, EM Science, Cherry Hill, NJ) operating at ca. 4 ml/min. until the column was dry. Washes of 1 ml H₂O - 0.5 ml MeOH - 1 ml H₂O were followed by elution with 1 ml

of extraction solvent. A 200 μ l sample of the eluant was injected onto a C-18 reversed phase analytical HPLC column, 5 μ m, 4.6 mm x 250 mm (e.g., Beckman #235335, LKB 2134-630 Spherisorb ODS-2) and eluted with a recycled mobile phase
5 run at ambient temperature and a flow rate of 0.5 ml/min (ca. 75 bar).

Mobile Phase: 0.02 M Na_2HPO_4 in 75/25(v/v) $\text{H}_2\text{O}/\text{MeOH}$ 0.007% SDS pH 3.5 (conc. H_3PO_4). The separated catecholamines were detected with a LKB 2143
10 electrochemical detector at a potential setting of 500 mV using a teflon flow cell spacer of 2.2 μ l and a time constant of 2 sec. Peak heights were measured and recorded along with the chromatogram tracing using a Spectra-Physics 4270 integrator. Sample runs were preceded by injection of
15 a mixture of calibration standards (200 μ l) containing 50 nM/L of epinephrine (Epi), norepinephrine (NE), dopamine (DA), and DHBA in extraction solvent. The peak heights for each sample run were corrected by dividing the peak height of the DHBA in the standard by the peak height of the DHBA
20 in each sample. The resulting factor (calculated for each sample) was used to correct for losses due to dilution, non-specific binding to the tissue precipitate, incomplete elution, etc. Concentrations were calculated by multiplying the peak heights for Epi, NE and DA by that
25 samples correction factor and then dividing this value by the peak height of the respective standard. When this number is multiplied by the concentration of the standard (in this case 50 nM/L) the concentration of the catecholamine in the homogenate is obtained. This value is
30 multiplied by the volume of the homogenate (determined previously) to get the total catecholamine content of the tissue expressed in moles/g tissue. The resolution and retention times for a mixture of standards run under the conditions described in the previous section are shown in
35 Table XXX.

TABLE XXX

	<u>Retention Time (min.)</u>	<u>Compound</u>
5	12.10	3,4-dihydroxylphenylacetic acid (DOPAC)
	18.24	norepinephrine (NE)
10	21.82	epinephrine (Epi)
	23.19	homovanillic acid (HVA)
15	30.56	dihydroxybenzylamine (DHBA)
	42.58	dopamine (DA)

The linear response to various standards run over a 100 fold concentration range was excellent with values for both the correlation coefficient (r) and the coefficient of determination (r -squared) being $>.9999$ for all standards, while the rank correlation (Spearman's rho) was 1.0. To confirm the precision and accuracy of the values, tissue analysis was performed on a control group of Sprague-Dawley rats. The cumulative results are within the range of values reported in the literature [(e.g. Racz, K. et al, J. Cardiovasc. Pharmacol., 8, 676 (1986)]. The precision in the efficiency of extraction measured by the addition of an internal standard (DHBA) was also excellent with a fractional efficiency of 0.779(SE=.066) for the kidney extraction and 0.771(SE=.083) for the heart extracts. Relative to vehicle administration, both the Ex. #859 conjugate and fusaric acid decreased kidney norepinephrine concentration; however, only fusaric acid decreased heart norepinephrine concentration (see Table XXXI and Figures 12 and 13). These data indicate that the Ex. #859 conjugate is renal selective with chronic infusion.

TABLE XXXIEffect of Fusaric Acid and Ex. #859 conjugate on Tissue
Norepinephrine Concentration Following 5 Days of Infusion

5

Tissue:	Kidney	Heart
10		<u>Vehicle (25 µL/hr)</u>
Norepinephrine: (pMol/g) (SD)	889 (72)	2,248 (164)
15		<u>Fusaric Acid (2.5 mg/hr)</u>
Norepinephrine: (pMol/g) (SD)	519 (42)	862 (147)
20		<u>Ex. #859 Conjugate (5 mg/hr)</u>
Norepinephrine: (pMol/g) (SD)	589 (54)	2,444 (534)

Assay XI: Intrarenal Administration of Fusaric Acid in Anesthetized Dogs

In one anesthetized dog, bolus doses of fusaric acid (0.1-5.0 mg/kg) were administered into the renal artery. Mean arterial pressure (MAP), renal blood flow (RBF) and urinary sodium excretion ($U_{Na}V$) were measured. Bolus intrarenal injection of isotonic saline or 0.1 mg/kg of fusaric acid had no effect on any measure; however, 0.5, 1.0, and 5.0 mg/kg fusaric acid caused dose-related increases in renal blood flow, but had no significant effect on mean arterial pressure or urinary sodium excretion (see Table XXXII).

15

TABLE XXXII

Effect of Intrarenal Injection of Fusaric Acid on Blood Pressure, Sodium Excretion and Renal Blood Flow in the Dog

Dose (mg/kg):	Saline	0.1	0.5	1.0	5.0
25 Δ RBF (ml/min):	0	0	+46	+58	+132
U _{Na} V (μ Eq/min):	42.8	21.2	23.8	21.1	34.8
30 MAP (mm Hg):	136	136	136	138	140

Similar results were also found in a second experiment where non-depressor doses of fusaric acid were infused into the renal arteries of two dogs (see Table XXXIII).

5

TABLE XXXIII

10 Effect of Intrarenal Infusion of Fusaric Acid
 on Blood Pressure, Sodium Excretion and Renal
 Blood Flow in the Dog

15	Infusion:	<u>Dog #1</u>		<u>Dog #2</u>	
		Fusaric Acid		Fusaric Acid	
		Saline (1.25 mg/kg/min)		Saline (0.75mg/kg/min)	
	Δ RBF (ml/min) :	140	240	236	315
20	U _{Na} V (μEq/min) :	95	82	44	13
	MAP (mm Hg) :	136	136	140	148

25 These data indicate that intrarenal administration of fusaric acid increases renal blood flow in anesthetized dogs without altering systemic mean arterial pressure.

Assay XII: Acute In Vivo Effects of Ex. #859 Conjugate

This experiment was run to determine the renal selectivity of conjugate of the invention in dogs. Male 5 mongrel dogs (15-20 kg/ n=8; Antech, Inc., Barnhard, MO) were anesthetized with sodium pentobarbital (30 mg/kg as i.v. bolus, and 4-6 mg/kg/hr infusion) and catheters were placed in the femoral veins for compound injection or pentobarbital infusion, and the femoral artery for arterial pressure 10 recording. An electromagnetic flow probe (Carolina Medical Electronics, Inc., King, NC) was placed around the left renal artery for measurement of renal blood flow. Renal blood flow and arterial pressure were recorded on a Gould chart recorder. After surgery, 20-30 minutes were allowed for variables to 15 stabilize. Then a 20 minute control measurement was followed by injection of Ex. #859 conjugate at doses of 20 and 60 mg/kg, i.v., to two different groups of dogs. Variables were monitored for the next three hours. Results are shown in Table XXXIV and Figures 14 and 15.

20

TABLE XXXIVRenal Selectivity of Ex. #859 Conjugate in Dogs

5

Time After Injection of Ex. #859 Conjugate

		Zero	1 Hour	2 Hour	3 Hour
<hr/>					
Mean Arterial					
10	Pressure (mmHg)				
	20 mg/kg	138±6	139±7	139±8	140±8
	60 mg/kg	123±3	124±1	126±3	127±10
<hr/>					
Renal Blood					
15	Flow (ml/min)				
	20 mg/kg	88±19	107±23	123±29	125±29
	60 mg/kg	131±21	145±21	168±28	176±32

Compositions of the Invention

- Also embraced within this invention is a class of pharmaceutical compositions comprising one or more conjugates described above in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The conjugates of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of the conjugates of the present invention required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art. The conjugates and composition may, for example, be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.
- For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of active ingredient from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable daily dose for a human may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.1 to 3000 mg/kg body weight, particularly from about 1 to 100 mg/kg body weight, may be appropriate.
- The active ingredient may also be administered by injection as a composition wherein, for example, saline,

dextrose solutions or water may be used as a suitable carrier. A suitable daily dose is from about 0.1 to 100 mg/kg body weight injected per day in multiple doses depending on the disease being treated.

5

A preferred daily dose would be from about 1 to 30 mg/kg body weight. Conjugates indicated for prophylactic therapy will preferably be administered in a daily dose generally in a range from about 0.1 mg to about 100 mg per 10 kilogram of body weight per day. A more preferred dosage will be a range from about 1 mg to about 100 mg per kilogram of body weight. Most preferred is a dosage in a range from about 1 to about 50 mg per kilogram of body weight per day. A suitable dose can be administered, in 15 multiple sub-doses per day. These sub-doses may be administered in unit dosage forms. Typically, a dose or sub-dose may contain from about 1 mg to about 100 mg of conjugate per unit dosage form. A more preferred dosage will contain from about 2 mg to about 50 mg of conjugate 20 per unit dosage form. Most preferred is a dosage form containing from about 3 mg to about 25 mg of active compound per unit dose.

The dosage regimen for treating a disease 25 condition with the conjugates and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular compound 30 employed, and thus may vary widely.

For therapeutic purposes, the conjugates of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of 35 administration. If administered per os, the conjugates may be admixed with lactose, sucrose, starch powder, cellulose

esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of conjugate in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The conjugates may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride solutions, and/or various buffer solutions. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. Appropriate dosages, in any given instance, of course depend upon the nature and severity of the condition treated, the route of administration, including the weight of the patient.

Representative carriers, diluents and adjuvants include for example, water, lactose, gelatin, starches, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols, petroleum jelly, etc. The pharmaceutical compositions may be made up in a solid form such as granules, powders or suppositories or in a liquid form such as solutions, suspensions or emulsions. The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional pharmaceutical adjuvants such as preservatives, stabilizers, wetting agents, emulsifiers, buffers, etc.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

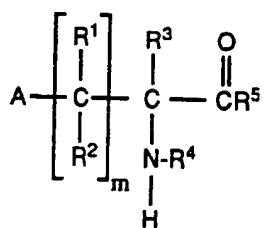
WHAT IS CLAIMED IS:

1. A conjugate comprising a first residue and a second residue, said first and second residues connected together by a cleavable bond, wherein said first residue is provided by an inhibitor compound capable of inhibiting biosynthesis of an adrenergic neurotransmitter, and wherein said second residue is capable of being cleaved from said first residue by an enzyme located predominantly in the kidney.

2. Conjugate of Claim 1 wherein said first and second residues are provided by precursor compounds wherein the precursor compound of one of said first and second residues has a reactable carboxylic acid moiety and the precursor of the other of said first and second residues has a reactable amino moiety or a moiety convertible to a reactable amino moiety, whereby a cleavable bond may be formed between said carboxylic acid moiety and said amino moiety.

3. Conjugate of Claim 2 wherein said inhibitor compound providing said first residue is selected from tyrosine hydroxylase inhibitor compounds, dopa-decarboxylase inhibitor compounds, dopamine- β -hydroxylase inhibitor compounds, and mimics of said inhibitor compounds.

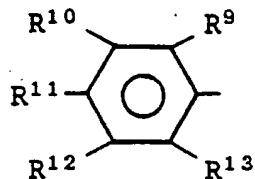
4. Conjugate of Claim 3 wherein said tyrosine hydroxylase inhibitor compound is of the formula



wherein each of R¹ through R³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, 5 amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R⁴ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, 10 carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein R⁵ is selected from -OR⁶ and

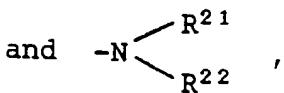
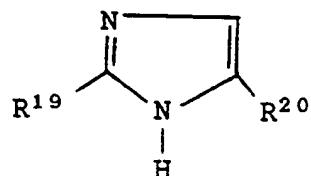
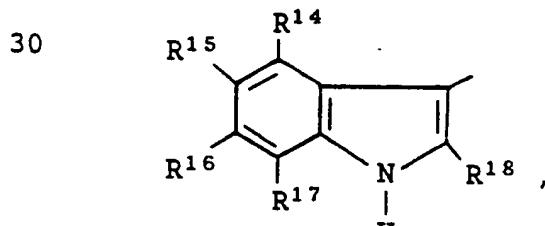
15 $\begin{array}{c} \text{R}^7 \\ | \\ -\text{N}- \\ | \\ \text{R}^8 \end{array}$, wherein R⁶ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl, and wherein each of R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, 20 haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; aralkyl; wherein m is a number selected 25 from zero through six;

wherein A is a phenyl ring of the formula



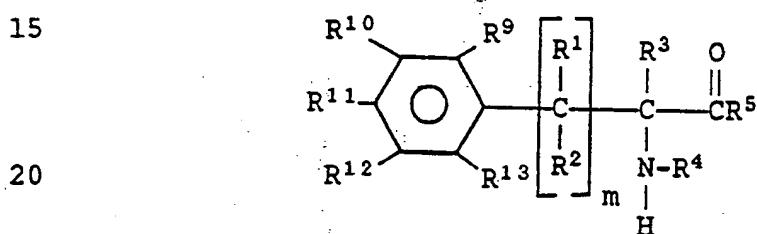
30 wherein each of R⁹ through R¹³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano,

amino, monoalkylamino, dialkylamino, carboxyl,
 carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl,
 alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl,
 aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy,
 5 carboxyalkoxy, formyl and a substituted or unsub-
 stituted 5- or 6-membered heterocyclic ring selected
 from the group consisting of pyrrol-1-yl, 2-carboxy-
 pyrrol-1-yl, imidazol-2-ylamino, indol-1-yl, carbozol-
 10 9-yl, 4,5-dihydro-4-hydroxy-4-trifluoromethylthiazol-
 3-yl, 4-trifluoromethylthiazol-2-yl, imidazol-2-yl
 and 4,5-dihydroimidazol-2-yl; wherein any two of the
 R⁹ through R¹³ groups may be taken together to form a
 15 benzoheterocyclic ring selected from the group consist-
 ing of indolin-5-yl, 1-(N-benzoylcaramimidoyl)indolin-
 5-yl, 1-carbamimidoylindolin-5-yl, 1H-2-oxindol-5-yl,
 insol-5-yl, 2-mercaptopbenzimidazol-5(6)-yl,
 2-aminobenzimidazol-5-(6)-yl, 2-methanesulfonamido-
 20 benzimidazol-5(6)-yl, 1H-benzoxanol-2-on-6-yl, 2-
 aminobenzothiazol-6-yl, 2-amino-4-mercaptopbenzothiazol-
 6-yl, 2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-2,2-dioxo-
 2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-1,3-dimethyl-
 2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 4-methyl-2(H)-
 25 oxoquinolin-6-yl, quinoxalin-6-yl, 2-hydroxyquinoxalin-
 6-yl, 2-hydroxquinolin-7-yl, 2,3-dihydroxyquinoxalin-
 6-yl and 2,3-dihydro-3(4H)-oxo-1,4-benzoxazin-7-yl;
 5-hydroxy-4H-pyran-4-on-2-yl, 2-hydroxypyrid-4-yl,
 2-aminopyrid-4-yl, 2-carboxypyrid-4-yl or tetrazolo-
 30 [1,5-a]pyrid-7-yl; and wherein A may be selected from

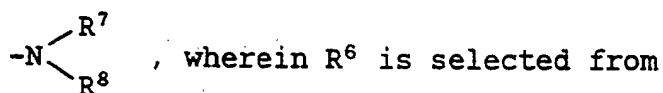


wherein each of R¹⁴ through R²⁰ is independently selected from hydrido, alkyl, hydroxy, hydroxyalkyl, alkoxy, cycloalkyl, cycloalkylalkyl, halo, haloalkyl, aryloxy, alkoxycarboxyl, aryl, aralkyl, cyano, 5 cyanoalkyl, amino, monoalkylamino and dialkylamino, wherein each of R²¹ and R²² is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, 10 cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; or a pharmaceutically-acceptable salt thereof.

5. Conjugate of Claim 4 wherein said inhibitor compound is of the formula



wherein each of R¹ and R² is hydrido; wherein m is one; wherein R³ is selected from alkyl, alkenyl and alkynyl; wherein R⁴ is selected from hydrido, alkyl, 25 cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein R⁵ is selected 30 from OR⁶ and



35 hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl and phenyl, and wherein each of R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl,

hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R⁹ through R¹³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxycarbonyl, alkoxycarbonyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, pyrrol-1-yl 2-carboxypyrrrol-1-yl, imidazol-2-ylamino, indol-1-yl, carbazol-9-yl, 4,5-dihydro-4-trifluoromethylthiazol-3-yl, 4-trifluoromethylthiazol-2-yl, imidazol-2-yl and 4,5-dihydroimidazol-2-yl, and wherein any two of the R⁹ through R¹³ groups may be taken together to form a benzoheterocyclic ring selected from the group consisting of indolin-5-yl, 1-(N-benzoylecarbamimidoyl)-indolin-5-yl, 1-carbamimidoylindolin-5-yl, 1H-2-oxindol-5-yl, indol-5-yl, 2-mercaptopbenzimidazol-5(6)-yl, 2-aminobenzimidazol-5-(6)-yl, 2-methanesulfonamido-benzimidazol-5(6)-yl, 1H-benzoxanol-2-on-6-yl, 2-amino-benzothiazol-6-yl, 2-amino-4-mercaptopbenzothiazol-6-yl, 2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-1,3-dimethyl-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 4-methyl-2(H)-oxoquinolin-6-yl, quinoxalin-6-yl, 2-hydroxyquinoxalin-6-yl, 2-hydroxyquinoxalin-7-yl, 2,3-dihydroxyquinoxalin-6-yl and 2,3-dihydro-3(4H)-oxo-1,4-benzoxazin-7-yl; wherein R⁵ is -CH=CH₂ or -C≡CH; wherein R⁶ is selected from hydrido, alkyl, hydroxy, hydroxyalkyl, alkoxy, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino; and wherein each of R⁷ and R⁸ independently is selected from hydrido, alkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; or a pharmaceutically-acceptable salt thereof.

6. Conjugate of Claim 5 wherein said inhibitor compound is selected from the group consisting of
- 4-cyanoamino- α -methylphenylalanine;
- 5 3-carboxy- α -methylphenylalanine;
- 3-cyano- α -methylphenylalanine methyl ester;
- α -methyl-4-thiocarbamoylphenylalanine methyl ester;
- 4-(aminomethyl)- α -methylphenylalanine;
- 4-guanidino- α -methylphenylalanine;
- 10 3-hydroxy-4-methanesulfonamido- α -methylphenylalanine;
- 3-hydroxy-4-nitro- α -methylphenylalanine;
- 4-amino-3-methanesulfonyloxy- α -methylphenylalanine;
- 3-carboxymethoxy-4-nitro- α -methylphenylalanine;
- α -methyl-4-amino-3-nitrophenylalanine;
- 15 3,4-diamino- α -methylphenylalanine;
- α -methyl-4-(pyrrol-1-yl)phenylalanine;
- 4-(2-aminoimidazol-1-yl)- α -methylphenylalanine;
- 4-(imidazol-2-ylamino)- α -methylphenylalanine;
- 4-(4,5-dihydro-4-hydroxy-4-trifluoromethyl-thiazol-2-yl)-
- 20 α -methylphenylalanine methyl ester;
- α -methyl-4-(4-trifluoromethylthiazol-2-yl)phenylalanine;
- α -methyl-3-(4-trifluoromethylthiazol-2-yl)-phenyl-
- alanine;
- 4-(imidazol-2-yl)- α -methylphenylalanine;
- 25 4-(4,5-dihydroimidazol-2-yl)- α -methylphenylalanine;
- 3-(imidazol-2-yl)- α -methylphenylalanine;
- 3-(4,5-dihydroimidazol-2-yl)- α -methylphenylalanine;
- 4-(imidazol-2-yl)phenylalanine;
- 4,5-dihydroimidazol-2-yl)phenylalanine;
- 30 3-(imidazol-2-yl)phenylalanine;
- 3-(2,3-dihydro-1H-indol-4-yl)- α -methylalanine;
- α -methyl-3-(1H-2-oxindol-5-yl)alanine;
- 3-[1-(N-benzoylcarbamimidoyl)-2,3-dihydro-1H-
- indol-5-yl]- α -methylalanine;
- 35 3-(1-carbamimidoyl-2,3-dihydro-1H-indol-5-yl- α -
- methylalanine;

3-(1H-indol-5-yl)- α -methylalanine;
3-(benzimidazol-2-thione-5-yl)- α -methylalanine;
3-(2-aminobenzimidazol-5-yl-2-methylalanine;
2-methyl-3-(benzoxazol-2-on-6-yl)alanine;
5 3-(2-aminobenzothiazol-6-yl)-2-methylalanine;
3-(2-amino-4-mercaptopbenzothiazol-6-yl)-2-
methylalanine;
3-(2-aminobenzothiazol-6-yl)alanine;
2-methyl-3-(2,1,3-benzothiadiazol-5-yl)alanine;
10 3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)-2-
methylalanine-2,2-dioxide;
3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)-2-methyl-
alanine-2,2-dioxide methyl ester;
3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)alanine
15 2,2-dioxide;
3-(1,3-dihydro-1,3-dimethylbenzo-2,1,3-thiadiazol-5-
yl)-2-methylalanine 2,2-dioxide;
 α -methyl-3-[4-methyl-2(1H)-oxoquinolin-6-yl]alanine;
3-[4-methyl-2(1H)-oxoquinolin-6-yl]alanine;
20 2-methyl-3-(quinoxalin-6-yl)alanine;
2-methyl-3-(2-hydroxyquinoxalin-6-yl)alanine;
2-methyl-3-(2-hydroxyquinoxalin-7-yl)alanine;
3-(2,3-dihydroxyquinoxalin-6-yl)-2-methylalanine;
3-(quinoxalin-6-yl)alanine;
25 3-(2,3-dihydroxyquinoxalin-6-yl)alanine;
3-(1,4-benzoxazin-3-one-6-yl)-2-methylalanine;
3-(1,4-benzoxazin-3-one-7-yl)alanine;
3-(5-hydroxy-4H-pyran-4-on-2-yl)-2-methylalanine;
3-(2-hydroxy-4-pyridyl)-2-methylalanine;
30 3-(2-carboxy-4-pyridyl)-2-methylamine;
 α -methyl-4-(pyrrol-1-yl)phenylalanine;
 α -ethyl-4-(pyrrol-1-yl)phenylalanine;
 α -propyl-4-(pyrrol-1-yl)phenylalanine;
4-[2-(carboxy)pyrrol-1-yl]phenylalanine;
35 α -methyl-4-(pyrrol-1-yl)phenylalanine;
3-hydroxy- α -methyl-4-(pyrrol-1-yl)phenylalanine;
3-methoxy- α -methyl-4-(pyrrol-1-yl)phenylalanine;

4-methoxy- α -methyl-3-(pyrrol-1-yl)phenylalanine;
4-(indol-1-yl)- α -methylphenylalanine;
4-(carbazol-9-yl)- α -methylphenylalanine;
2-methyl-3-(2-methanesulfonylamidobenzimidazol-
5 5-yl)alanine;
2-methyl-3-(2-amino-4-pyridyl)alanine;
2-methyl-3[tetrazolo-(1,5)- α -pyrid-7-yl]alanine;
D,L- α -methyl- β -(4-hydroxy-3-methyl)phenylalanine;
D,L- α -methyl- β -(4-hydroxy-3-phenyl)phenylalanine;
10 D,L- α -methyl- β -(4-hydroxy-3-benzyl)phenylalanine;
D,L- α -methyl- β -(4-methoxy-3-cyclohexyl)phenyl-
alanine;
 α , β , β -trimethyl- β -(3,4-dihydroxyphenyl)alanine;
 α , β , β -trimethyl- β -(4-hydroxyphenyl)alanine;
15 N-methyl- α , β , β -trimethyl- β -(3,4-dihydroxyphenyl)-
alanine;
D,L- α , β , β -trimethyl- β -(3,4-dihydroxyphenyl)alanine;
 α , β , β -trimethyl- β -(3,4-dimethoxyphenyl)alanine;
L- α -methyl- β -3,4-dihydroxyphenylalanine;
20 L- α -ethyl- β -3,4-dihydroxyphenylalanine;
L- α -propyl- β -3,4-dihydroxyphenylalanine;
L- α -butyl- β -3,4-dihydroxyphenylalanine;
L- α -methyl- β -2,3-dihydroxyphenylalanine;
L- α -ethyl- β -2,3-dihydroxyphenylalanine;
25 L- α -propyl- β -2,3-dihydroxyphenylalanine;
L- α -butyl- β -2,3-dihydroxyphenylalanine;
L- α -methyl-4-chloro-2,3-dihydroxyphenylalanine;
L- α -ethyl-4-chloro-2,3-dihydroxyphenylalanine;
L- α -propyl-4-chloro-2,3-dihydroxyphenylalanine;
30 L- α -butyl-4-chloro-2,3-dihydroxyphenylalanine;
L- α -ethyl- β -4-methyl-2,3-dihydroxyphenylalanine;
L- α -methyl- β -4-methyl-2,3-dihydroxyphenylalanine;
L- α -propyl- β -4-methyl-2,3-dihydroxyphenylalanine;
L- α -butyl- β -4-methyl-2,3-dihydroxyphenylalanine;
35 L- α -methyl- β -4-fluoro-2,3-dihydroxyphenylalanine;
L- α -ethyl- β -4-fluoro-2,3-dihydroxyphenylalanine;
L- α -propyl- β -4-fluoro-2,3-dihydroxyphenylalanine;

- L- α -butyl- β -4-fluoro-2,3-dihydroxyphenylalanine;
L- α -methyl- β -4-trifluoromethyl-2,3-dihydroxyphenyl-
alanine
5 L- α -ethyl- β -4-trifluoromethyl-2,3-dihydroxyphenyl-
alanine
L- α -propyl- β -4-trifluoromethyl-2,3-dihydroxyphenyl-
alanine
L- α -butyl- β -4-trifluoromethyl-2,3-dihydroxyphenyl-
alanine
10 L- α -methyl- β -3,5-dihydroxyphenylalanine;
L- α -ethyl- β -3,5-dihydroxyphenylalanine;
L- α -propyl- β -3,5-dihydroxyphenylalanine;
L- α -butyl- β -3,5-dihydroxyphenylalanine;
L- α -methyl- β -4-chloro-3,5-dihydroxyphenylalanine;
15 L- α -ethyl- β -4-chloro-3,5-dihydroxyphenylalanine;
L- α -propyl- β -4-chloro-3,5-dihydroxyphenylalanine;
L- α -butyl- β -4-chloro-3,5-dihydroxyphenylalanine;
L- α -methyl- β -4-fluoro-3,5-dihydroxyphenylalanine;
L- α -ethyl- β -4-fluoro-3,5-dihydroxyphenylalanine;
20 L- α -propyl- β -4-fluoro-3,5-dihydroxyphenylalanine;
L- α -butyl- β -4-fluoro-3,5-dihydroxyphenylalanine;
L- α -methyl- β -4-trifluoromethyl-3,5-dihydroxyphenyl-
alanine;
L- α -ethyl- β -4-trifluoromethyl-3,5-dihydroxyphenyl-
25 alanine;
L- α -propyl- β -4-trifluoromethyl-3,5-dihydroxyphenyl-
alanine;
L- α -butyl- β -4-trifluoromethyl-3,5-dihydroxyphenyl-
alanine;
30 L- α -methyl-2,5-dihydroxyphenylalanine;
L- α -ethyl-2,5-dihydroxyphenylalanine;
L- α -propyl-2,5-dihydroxyphenylalanine;
L- α -butyl-2,5-dihydroxyphenylalanine;
L- α -methyl- β -4-chloro-2,5-dihydroxyphenylalanine;
35 L- α -ethyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -propyl- β -4-chloro-2,5-dihydroxyphenylalanine;

L- α -butyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -methyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -ethyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -propyl- β -4-chloro-2,5-dihydroxyphenylalanine;
5 L- α -butyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -methyl- β -methyl-2,5-dihydroxyphenylalanine;
L- α -ethyl- β -methyl-2,5-dihydroxyphenylalanine;
L- α -propyl- β -methyl-2,5-dihydroxyphenylalanine;
L- α -butyl- β -methyl-2,5-dihydroxyphenylalanine;
10 L- α -methyl- β -4-trifluoromethyl-2,5-dihydroxyphenyl-
alanine;
L- α -ethyl- β -4-trifluoromethyl-2,5-dihydroxyphenyl-
alanine;
L- α -propyl- β -4-trifluoromethyl-2,5-dihydroxyphenyl-
15 alanine;
L- α -butyl- β -4-trifluoromethyl-2,5-dihydroxyphenyl-
alanine;
L- α -methyl- β -3,4,5-trihydroxyphenylalanine;
L- α -ethyl- β -3,4,5-trihydroxyphenylalanine;
20 L- α -propyl- β -3,4,5-trihydroxyphenylalanine;
L- α -butyl- β -3,4,5-trihydroxyphenylalanine;
L- α -methyl- β -2,3,4-trihydroxyphenylalanine;
L- α -ethyl- β -2,3,4-trihydroxyphenylalanine;
L- α -propyl- β -2,3,4-trihydroxyphenylalanine;
25 L- α -butyl- β -2,3,4-trihydroxyphenylalanine;
L- α -methyl- β -2,4,5-trihydroxyphenylalanine;
L- α -ethyl- β -2,4,5-trihydroxyphenylalanine;
L- α -propyl- β -2,4,5-trihydroxyphenylalanine;
L- α -butyl- β -2,4,5-trihydroxyphenylalanine;
30 L-phenylalanine;
D,L- α -methylphenylalanine;
D,L-3-iodophenylalanine;
D,L-3-iodo- α -methylphenylalanine;
3-iodotyrosine;
35 3,5-diiodotyrosine;
L- α -methylphenylalanine;

D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)alanine;
D,L- α -methyl- β -(4-methoxy-3-benzylphenyl)alanine;
D,L- α -methyl- β -(4-hydroxy-3-benzylphenyl)alanine;
D,L- α -methyl- β -(4-methoxy-3-cyclohexylphenyl)alanine;
5 D,L- α -methyl- β -(4-hydroxy-3-cyclohexylphenyl)alanine;
D,L- α -methyl- β -(4-methoxy-3-methylphenyl)alanine;
D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)alanine;
N,O-dibenzoyloxycarbonyl-D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)alanine;
10 N,O-dibenzoyloxycarbonyl-D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)alanine amide;
D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)-alanine amide;
N,O-diacyetyl-D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)alanine;
15 D,L-N-acetyl- α -methyl- β -(4-hydroxy-3-methylphenyl)-alanine;
L-3,4-dihydroxy- α -methylphenylalanine;
L-4-hydroxy-3-methoxy- α -methylphenylalanine;
20 L-3,4-methylene-dioxy- α -methylphenylalanine;
2-vinyl-2-amino-3-(2-methoxyphenyl)propionic acid;
2-vinyl-2-amino-3-(2,5-dimethoxyphenyl)propionic acid;
2-vinyl-2-amino-3-(2-imidazolyl)propionic acid;
25 2-vinyl-2-amino-3-(2-methoxyphenyl)propionic acid ethyl ester;
 α -methyl- β -(2,5-dimethoxyphenyl)alanine;
 α -methyl- β -(2,5-dihydroxyphenyl)alanine;
 α -ethyl- β -(2,5-dimethoxyphenyl)alanine;
30 α -ethyl- β -(2,5-dihydroxyphenyl)alanine;
 α -methyl- β -(2,4-dimethoxyphenyl)alanine;
 α -methyl- β -(2,4-dihydroxyphenyl)alanine;
 α -ethyl- β -(2,4-dimethoxyphenyl)alanine;
35 α -ethyl- β -(2,4-dihydroxyphenyl)alanine;
 α -methyl- β -(2,5-dimethoxyphenyl)alanine ethyl ester;
2-ethynyl-2-amino-3-(3-indolyl)propionic acid;

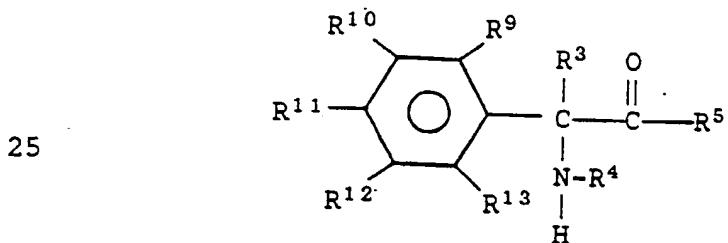
2-ethynyl-2,3-(2-methoxyphenyl)propionic acid;
2-ethynyl-2,3-(5-hydroxyindol-3-yl)propionic acid;
2-ethynyl-2-amino-3-(2,5-dimethoxyphenyl)propionic acid;
2-ethynyl-2-amino-3-(2-imidazolyl)propionic acid;
5 2-ethynyl-2-amino-3-(2-methoxyphenyl)propionic acid
ethyl ester;
3-carbomethoxy-3-(4-benzyloxybenzyl)-3-aminoprop-1-yne;
 α -ethynyltyrosine hydrochloride;
 α -ethynyltyrosine;
10 α -ethynyl-m-tyrosine;
 α -ethynyl- β -(2-methoxyphenyl)alanine;
 α -ethynyl- β -(2,5-dimethoxyphenyl)alanine; and
 α -ethynylhistidine.

7. Conjugate of Claim 5 wherein at least
15 one of R¹⁰, R¹¹ and R¹² is selected from hydroxy,
alkoxy, aryloxy, aralkoxy and alkoxycarbonyl.

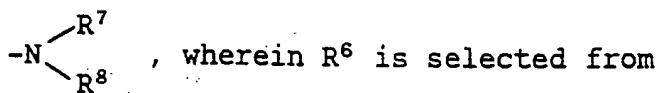
8. Conjugate of Claim 7 wherein said
inhibitor compound is selected from the group
consisting of
20 α -methyl-3-(pyrrol-1-yl)tyrosine;
 α -methyl-3-(4-trifluoromethylthiazol-2-yl)tyrosine;
3-(imidazol-2-yl)- α -methyltyrosine;
L- α -methyl-m-tyrosine;
L- α -ethyl-m-tyrosine;
25 L- α -propyl-m-tyrosine;
L- α -butyl-m-tyrosine;
L- α -methyl-p-chloro-m-tyrosine;
L- α -ethyl-p-chloro-m-tyrosine;
L- α -butyl-p-chloro-m-tyrosine;
30 L- α -methyl-p-bromo-m-tyrosine;
L- α -ethyl-p-bromo-m-tyrosine;
L- α -butyl-p-bromo-m-tyrosine;
L- α -methyl-p-fluoro-m-tyrosine;
L- α -methyl-p-iodo-m-tyrosine;

L- α -ethyl-p-iodo-m-tyrosine;
L- α -methyl-p-methyl-m-tyrosine;
L- α -methyl-p-ethyl-m-tyrosine;
L- α -ethyl-p-ethyl-m-tyrosine;
5 L- α -ethyl-p-methyl-m-tyrosine;
L- α -methyl-p-butyl-m-tyrosine;
L- α -methyl-p-trifluoromethyl-m-tyrosine;
L-3-iodotyrosine;
L-3-chlorotyrosine;
10 L-3,5-diiodotyrosine;
L- α -methyltyrosine;
D,L- α -methyltyrosine;
D,L-3-iodo- α -methyltyrosine;
L-3-bromo- α -methyltyrosine;
15 D,L-3-bromo- α -methyltyrosine;
L-3-chloro- α -methyltyrosine;
D,L-3-chloro- α -methyltyrosine; and
2-vinyl-2-amino-3-(4-hydroxyphenyl)propionic acid.

9. Conjugate of Claim 4 wherein said
20 inhibitor compound is of the formula



wherein R³ is selected from alkyl, alkenyl and alkynyl;
wherein R⁴ is selected from hydrido, alkyl, cycloalkyl,
30 hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl,
aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl,
amino, cyanoamino, monoalkylamino, dialkylamino,
alkylsulfinyl, alkylsulfonyl, arylsulfinyl and
arylsulfonyl; wherein m is a number selected from
35 zero through five, inclusive; wherein R⁵ is selected
from OR⁶ and

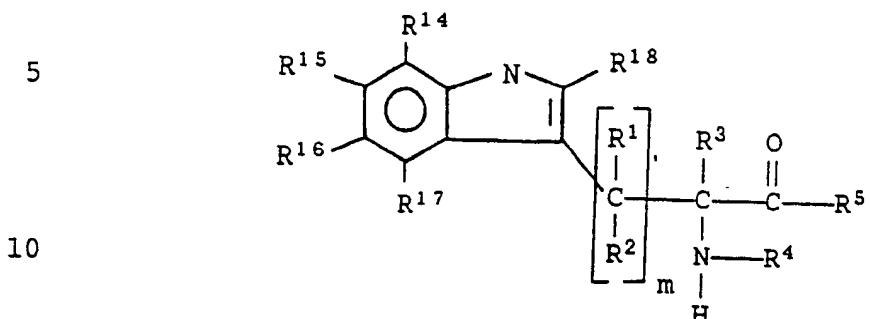


hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl
5 and phenyl, and wherein each of R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino,
10 alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R⁹ through R¹³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxycarbonyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl,
15 alkoxycarbonyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

10. Conjugate of Claim 9 wherein at least one of R¹⁰, R¹¹ and R¹² is selected from hydroxy, alkoxy, aryloxy, aralkoxy and alkoxycarbonyl.
20

11. Conjugate of Claim 10 wherein said inhibitor compound is selected from the group consisting of methyl(+)-2-(4-hydroxyphenyl)glycinate; isopropyl and 3-methyl butyl esters of (+)-2-(4-hydroxyphenyl)-
25 glycine; (+)-2-(4-hydroxyphenyl)glycine; (-)-2-(4-hydroxyphenyl)glycine; (+)-2-(4-methoxyphenyl)-glycine; and (+)-2-(4-hydroxyphenyl)glycinamide.

12. Conjugate of Claim 4 wherein said inhibitor compound is of the formula



wherein each of R¹ and R² is hydrido; wherein R³ is selected from alkyl, alkenyl and alkynyl; wherein R⁴ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein m is a number selected from zero through five, inclusive; wherein each of R¹⁴ through R¹⁷ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cyclo-alkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy and formyl.

30 13. Conjugate of Claim 12 wherein said inhibitor compound is selected from the group consisting of
 L- α -methyltryptophan;
 D,L-5-methyltryptophan;
 35 D,L-5-chlorotryptophan;
 D,L-5-bromotryptophan;

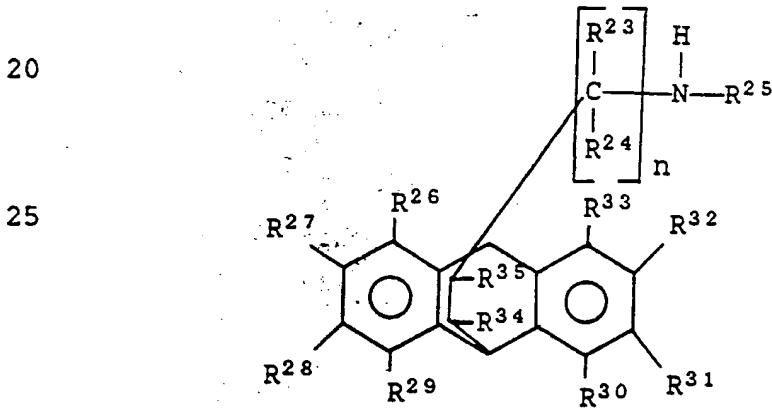
- D,L-5-iodotryptophan;
 L-5-hydroxytryptophan;
 D,L-5-hydroxy- α -methyltryptophan;
 α -Ethynyltryptophan;
 5 5-Methoxymethoxy- α -ethynyltryptophan; and
 5-Hydroxy- α -ethynyltryptophan.

14. Conjugate of Claim 4 wherein A is

10 $\begin{array}{c} R^{21} \\ | \\ -N- \\ | \\ R^{22} \end{array}$, and m is a number selected from zero to
 three, inclusive.

15 15. Conjugate of Claim 14 wherein said
 inhibitor compound is selected from the group consisting
 of 2-vinyl-2-amino-5-aminopentanoic acid and
 2-ethynyl-2-amino-5-aminopentanoic acid.

16. Conjugate of Claim 4 wherein said
 inhibitor compound is of the formula

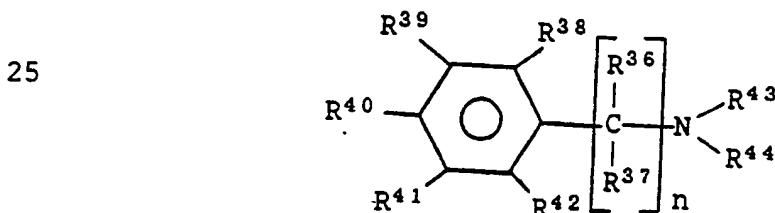


30 wherein each of R²³ and R²⁴ is independently
 selected from hydrido, hydroxy, alkyl, cycloalkyl,
 cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy,
 aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo,
 cyano, amino, monoalkylamino, dialkylamino, carboxy,

carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R²⁵ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxy carbonyl, 5 carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R²⁶ through R³⁵ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, 10 aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, 15 nitro, alkylsulfonyloxy, alkoxy and formyl; wherein n is a number selected from zero to five, inclusive; or a pharmaceutically-acceptable salt thereof.

17. Conjugate of Claim 16 wherein said inhibitor compound is benzoctamine.

20 18.. Conjugate of Claim 3 wherein said inhibitor compound is a dopa-decarboxylase inhibitor of the formula



30 35 wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl,

alkynyl, cyanoamino, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy and formyl; wherein n is a whole number from zero through four; wherein each of R⁴³ and R⁴⁴ is
5 independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl,
10 arylsulfinyl, arylsulfonyl, alkenyl, cycloalkenyl and alkynyl, with the proviso that R⁴³ and R⁴⁴ cannot both be carboxyl at the same time, and with the further proviso that at least one of R⁴³ through R⁴⁴
15 is a primary or secondary amino group; or a pharmaceutically-acceptable salt thereof.

19. Conjugate of Claim 18 wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl; wherein n is a whole number from one through three; wherein
20 each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl and alkanoyl.
25

30 20. Conjugate of Claim 19 wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, benzyl, phenyl, alkoxy, benzyloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, cyanoamino, cyano,
35

aminomethyl, carboxyl, carboxyalkoxy and formyl; wherein n is one or two; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, benzyl, phenyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, 5 amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl and alkanoyl.

21. Conjugate of Claim 20 wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, alkoxy, haloalkyl, 10 hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl, aminomethyl, carboxyalkoxy and formyl; wherein n is one or two; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, 15 carboxyl and carboxyalkyl.

22. Conjugate of Claim 21 wherein each of R³⁶ and R⁴² is hydrido and n is one; wherein each of R³⁸ through R⁴² is independently selected from hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, 20 monoalkylamino, carboxyl, carboxyalkyl, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl and carboxyalkyl.

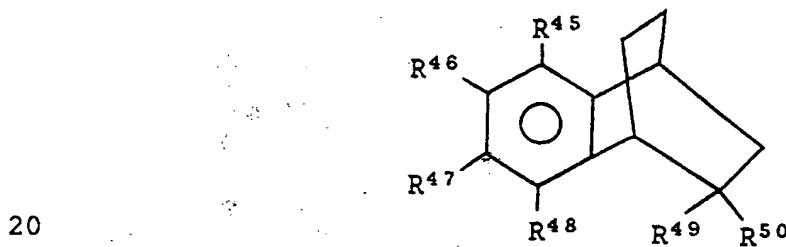
25 23. Conjugate of Claim 22 wherein said inhibitor compound is selected from (2,3,4-trihydroxy)benzylhydrazine; 1-(D,L-seryl-2-(2,3,4-trihydroxybenzyl)hydrazine; and 1-(3-hydroxylbenzyl)-1-methylhydrazine.

30 24. Conjugate of Claim 21 wherein each of R³⁶ and R³⁷ is independently selected from hydrido, alkyl and amino and n is two; wherein each of R³⁸

through R⁴² is independently selected from hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl and carboxyalkyl.

25. Conjugate of Claim 24 wherein said inhibitor compound is selected from
 10 2-hydrazino-2-methyl-3-(3,4-dihydroxyphenyl)propionic acid; α -(monofluoromethyl)dopa and α -(difluoromethyl)-dopa.

26. Conjugate of Claim 3 wherein said inhibitor compound is a dopa-decarboxylase inhibitor
 15 of the formula



wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy and formyl;
 25 wherein each of R⁴⁹ and R⁵⁰ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl,

cyano, amino, monoalkylamino, dialkylamino, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl and

5 O
 ||
-CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy, aryloxy, aralkoxy, amino, monoalkylamino and dialkylamino; with the proviso that R⁴⁹ and R⁵⁰ cannot both be carboxyl at the same time, and with the further
10 proviso that at least one of R⁴⁵ through R⁴⁸ is a primary or secondary amino group or a carboxyl group; or a pharmaceutically-acceptable salt thereof.

27. Conjugate of Claim 26 wherein each of R⁴⁵ through R⁴⁸ is independently selected from
15 hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl; wherein
20 each of R⁴⁹ and R⁵⁰ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyalkyl and
25 alkanoyl and

30 O
 ||
-CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy, phenoxy, benzyloxy, amino, monoalkylamino and dialkylamino.

28. Conjugate of Claim 27 wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, benzyl, phenyl, alkoxy, benzyloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyl,

carboxyalkyl, alkanoyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴⁹ and R⁵⁰ is independently selected from hydrido, alkyl, benzyl, phenyl, alkoxyalkyl, 5 haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyalkyl and alkanoyl and

10 O
 ||
-CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy, amino and monoalkylamino.

29. Conjugate of Claim 28 wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, 15 monoalkylamino, carboxyl, carboxyalkyl aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴⁹ and R⁵⁰ is independently selected from hydrido alkyl, amino, monoalkylamino, carboxyalkyl and

20 O
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-CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy, amino and monoalkylamino.

30. Conjugate of Claim 29 wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, alkoxy and hydroxyalkyl; 25 wherein each of R⁴⁹ and R⁵⁰ is independently selected from alkyl, amino, monoalkylamino, and

30 O
 ||
-CR⁵¹ wherein R⁵¹ is selected from hydroxy, methoxy, ethoxy, propoxy, butoxy, amino, methylamino and ethylamino.

31. Conjugate of Claim 30 wherein said inhibitor compound is selected from endo-2-amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylic acid;

5 ethyl-endo-2-amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylate hydrochloride; exo-2-amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylic acid; and

10 ethyl-exo-2-amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylate hydrochloride.

32. Conjugate of Claim 3 wherein said inhibitor compound is a dopa-decarboxylase inhibitor selected from

2,3-dibromo-4,4-bis(4-ethylphenyl)-2-butenoic acid;

15 3-bromo-4-(4-methoxyphenyl)-4-oxo-2-butenoic acid; N-(5'-phosphopyridoxyl)-L-3,4-dihydroxyphenylalanine; N-(5'-phosphopyridoxyl)-L-m-aminotyrosine; D,L-β-(3,4-dihydroxyphenyl)lactate; D,L-β-(5-hydroxyindolyl-3)lactate;

20 2,4-dihydroxy-5-(1-oxo-2-propenyl)benzoic acid; 2,4-dimethoxy-5-[1-oxo-3-(2,3,4-trimethoxyphenyl-2-propenyl]benzoic acid;

25 2,4-dihydroxy-5-[1-oxo-3-(2-thienyl)-2-propenyl]benzoic acid; 2,4-dihydroxy-5-[3-(4-hydroxyphenyl)-1-oxo-2-propenyl]benzoic acid;

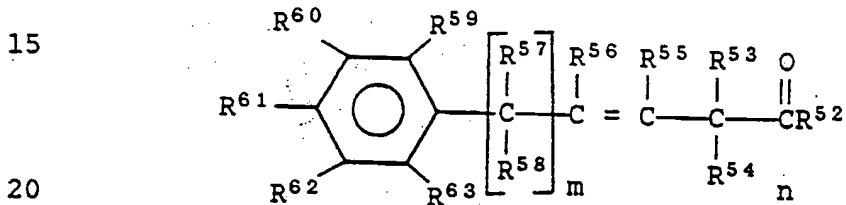
30 5-[3-(4-chlorophenyl)-1-oxo-2-propenyl]-2,4-dihydroxybenzoic acid; 2,4-dihydroxy-5-(1-oxo-3-phenyl-2-propenyl)benzoic acid;

* 2,4-dimethoxy-5-[1-oxo-3-(4-pyridinyl)-2-propenyl]benzoic acid;

35 5-[3-(3,4-dimethoxyphenyl)-1-oxo-2-propenyl]-2,4-dimethoxybenzoic acid; 2,4-dimethoxy-5-(1-oxo-3-phenyl-2-propenyl)benzoic acid;

- 5-[3-(2-furanyl)-1-oxo-2-propenyl]-2,4-dimethoxy benzoic acid;
- 2,4-dimethoxy-5-[1-oxo-3-(2-thienyl)-2-propenyl] benzoic acid;
- 5 2,4-dimethoxy-5-[3-(4-methoxyphenyl)-1-oxo-2-propenyl] benzoic acid;
- 5-[3-(4-chlorophenyl)-1-oxo-2-propenyl]-2,4-dimethoxy benzoic acid; and
- 10 5-[3-[4-(dimethylamino)phenyl]-1-oxo-2-propenyl]-2,4-dimethoxy benzoic acid.

33. Conjugate of Claim 3 wherein said inhibitor compound is a dopa-decarboxylase inhibitor of the formula:



- wherein R⁵² is selected from hydrido, OR⁶⁴ and
 $\begin{array}{c} R^{65} \\ \diagdown \\ -N \\ \diagup \\ R^{66} \end{array}$, wherein R⁶⁴ is selected from
25 hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl and phenyl, and wherein each of R⁶⁵ and R⁶⁶ is independently selected from hydrido, alkyl, alkanoyl, amino, monoalkylamino, dialkylamino, phenyl and phenalkyl; wherein each of R⁵³, R⁵⁴ and R⁵⁷
30 through R⁶³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxycarbonyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein each of R⁵⁵ and R⁵⁶ is independently

selected from hydrido, alkyl, cycloalkyl,
cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl,
haloalkyl, hydroxyalkyl and carboxyalkyl; wherein
each of m and n is a number independently selected
5 from zero through six, inclusive; or a
pharmaceutically-acceptable salt thereof.

34. Conjugate of Claim 33 wherein R⁵²
is OR⁶⁴ wherein R⁶⁴ is selected from hydrido, alkyl,
cycloalkyl, cycloalkylalkyl, benzyl and phenyl;
10 wherein each of R⁵³, R⁵⁴ and R⁵⁷ through R⁶³ is
independently selected from hydrido, alkyl,
cycloalkyl, hydroxy, alkoxy, benzyl and phenyl;
wherein each of R⁵⁵ and R⁵⁶ is independently selected
15 from hydrido, alkyl, cycloalkyl, benzyl and phenyl;
wherein each of m and n is a number independently
selected from zero through three, inclusive.

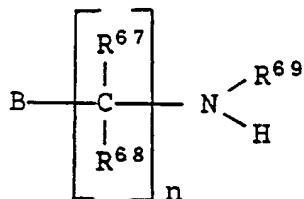
35. Conjugate of Claim 34 wherein R⁵²
is OR⁶⁴ wherein R⁶⁴ is selected from hydrido and
lower alkyl; wherein each of R⁵³ through R⁵⁸ is
20 hydrido; wherein each of R⁵⁹ through R⁶³ is
independently selected from hydrido, alkyl, hydroxy
and alkoxy, with the proviso that two of the R⁵⁹
through R⁶³ substituents are hydroxy; wherein each of
m and n is a number independently selected from zero
25 through two, inclusive.

36. Conjugate of Claim 35 which is
3-(3,4-dihydroxyphenyl)-2-propenoic acid.

37. Conjugate of Claim 26 wherein said dopa-decarboxylase inhibitor is a compound selected from amino-haloalkyl-hydroxyphenyl propionic acids; alpha-halomethyl-phenylalanine derivatives; and indole-substituted halomethylamino acids.

38. Conjugate of Claim 26 wherein said dopa-decarboxylase inhibitor is a compound selected from isoflavone extracts from fungi and streptomyces; sulfinyl substituted dopa and tyrosine derivatives; hydroxycoumarin derivatives; 1-benzylcyclobutenyl alkyl carbamate derivatives; aryl/thienyl-hydroxylamine derivatives; and β -2-substituted-cyclohepta-pyrrol-8-1H-on-7-yl alanine derivatives.

39. Conjugate of Claim 3 wherein said dopamine- β -hydroxylase inhibitor compound is of the formula



wherein B is selected from an ethylenic moiety, an acetylenic moiety and an ethylenic or acetylenic moiety substituted with one or more radicals selected from substituted or unsubstituted alkyl, aryl and heteroaryl; wherein each of R⁶⁷ and R⁶⁸ is independently selected from hydrido and alkyl; wherein R⁶⁹ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxy carbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is a number selected from one through five.

40. Conjugate of Claim 39 wherein B is an ethylenic or an acetylenic moiety substituted with an aryl or heteroaryl radical; and wherein n is a number from one through three.

41. Conjugate of Claim 39 wherein B is an ethylenic or acetylenic moiety incorporating carbon atoms in the beta- and gamma-positions relative to the nitrogen atom; and wherein n is one.

5 42. Conjugate of Claim 41 wherein said ethylenic or acetylenic moiety is substituted at the gamma carbon with an aryl or heteroaryl radical.

10 43. Conjugate of Claim 42 wherein said aryl radical is selected from phenyl, 2-thiophene, 3-thiophene, 2-furanyl, 3-furanyl, oxazolyl, thiazolyl and isoxazolyl, any one of which radicals may be substituted with one or more groups selected from halo, hydroxyl, alkyl, haloalkyl, cyano, alkoxy, alkoxyalkyl and cycloalkyl.

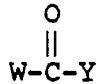
15 44. Conjugate of Claim 43 wherein said aryl radical is selected from phenyl, hydroxyphenyl, 2-thiophene and 2-furanyl; and wherein each of R⁶⁷, R⁶⁸ and R⁶⁹ is hydrido.

20 45. Conjugate of Claim 44 wherein said inhibitor compound is selected from the group consisting of
3-amino-2-(2'-thienyl)propene;
3-amino-2-(2'-thienyl)butene;
3-(N-methylamino)-2-(2'-thienyl)propene;
25 3-amino-2-(3'-thienyl)propene;
3-amino-2-(2'-furanyl)propene;
3-amino-2-(3'-furanyl)propene;
1-phenyl-3-aminopropyne; and
3-amino-2-phenylpropene.

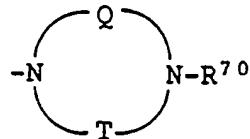
46. Conjugate of Claim 44 wherein said inhibitor compound is selected from the group consisting of

- (±)4-amino-3-phenyl-1-butyne;
- 5 (±)4-amino-3-(3'-hydroxyphenyl)-1-butyne;
- (±)4-amino-3-(4'-hydroxyphenyl)-1-butyne;
- (±)4-amino-3-phenyl-1-butene;
- (±)4-amino-3-(3'-hydroxyphenyl)-1-butene; and
- (±)4-amino-3-(4'-hydroxyphenyl)-1-butene.

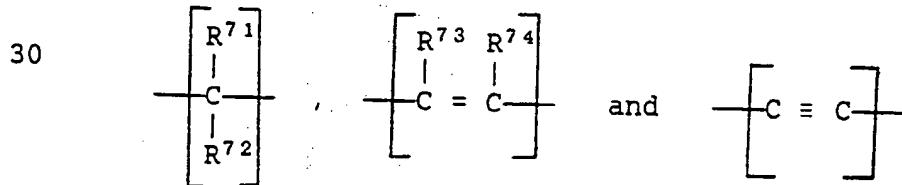
10 47. Conjugate of Claim 3 wherein said inhibitor compound is of the formula



15 wherein W is selected from alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl; wherein Y is selected from

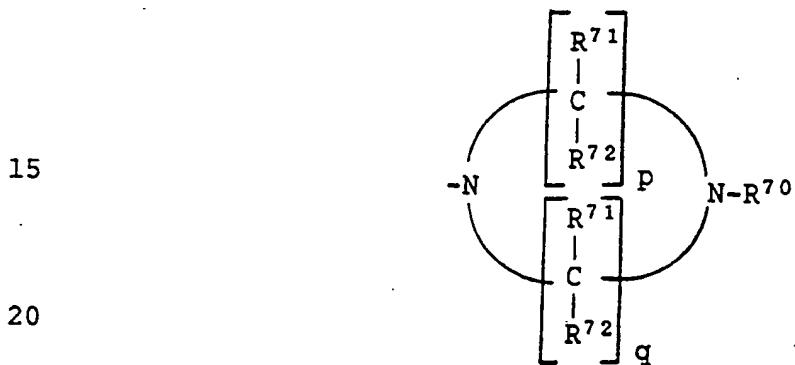


20 wherein R⁷⁰ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxy carbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of Q and T is one or more groups independently selected from



wherein each of R⁷¹ through R⁷⁴ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; or a pharmaceutically-acceptable salt thereof.

48. Conjugate of Claim 47 wherein W is
10 heteroaryl and Y is



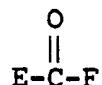
wherein R⁷⁰ is selected from hydrido, alkyl, amino, monoalkylamino, dialkylamino, phenyl and phenalkyl; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive.

49. Conjugate of Claim 48 wherein R⁷⁰ is selected from hydrido, alkyl, amino and monoalkylamino; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive.

50. Conjugate of Claim 49 wherein R⁷⁰ is selected from hydrido, alkyl and amino; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three.

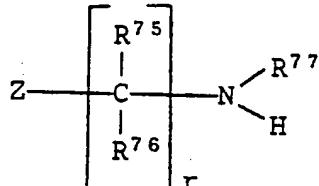
5 51. Conjugate of Claim 50 wherein R⁷⁰ is hydrido; wherein each of R⁷¹ and R⁷² is hydrido; and wherein each of p and q is two.

10 52. Conjugate of Claim 3 wherein said inhibitor compound is of the formula



15 wherein E is selected from alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl; wherein F is selected from

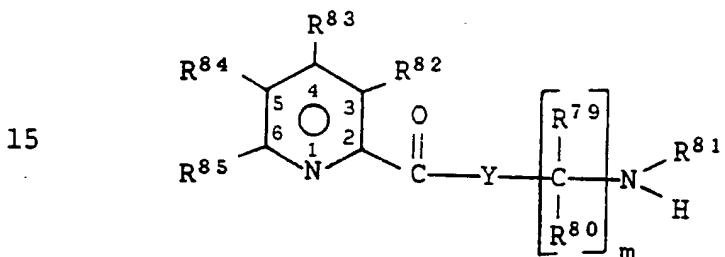
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25 wherein Z is selected from O, S and N-R⁷⁸; wherein each of R⁷⁵ and R⁷⁶ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, minoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R⁷⁵ and R⁷⁶ may form oxo or thio; wherein r is a number selected from zero through six, inclusive; wherein each of R⁷⁷ and R⁷⁸

is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, 5 dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; or a pharmaceutically-acceptable salt thereof.

10 53. Conjugate of Claim 3 wherein said dopamine- β -hydroxylase inhibitor compound is of the formula



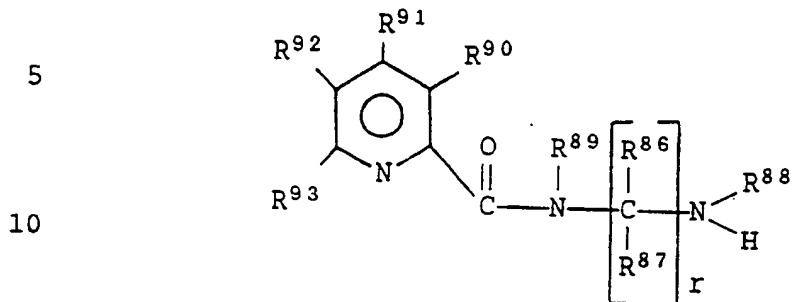
15 wherein each of R⁸² through R⁸⁵ is independently selected from hydrido, alkyl, haloalkyl, mercapto, alkylthio, cyano, alkoxy, alkoxyalkyl and cycloalkyl; 20 wherein Y is selected from oxygen atom and sulfur atom; wherein each of R⁷⁹ and R⁸⁰ is independently selected from hydrido and alkyl; wherein R⁵⁹ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, 25 haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; 30 and wherein m is a number from one through six; or a pharmaceutically-acceptable salt thereof.

35 54. Conjugate of Claim 53 wherein each of R⁸² through R⁸⁵ is independently selected from hydrido, alkyl and haloalkyl; wherein Y is selected from oxygen atom or nitrogen atom; wherein each of R⁷⁹,

R^{80} and R^{81} is independently hydrido and alkyl; and wherein m is a number selected from one through four, inclusive.

- 5 55. Conjugate of Claim 54 wherein said inhibitor compound is selected from aminomethyl-5-n-butylthiopicolinate; aminomethyl-5-n-butylpicolinate; 2'-aminoethyl-5-n-butylthiopicolinate; 2'-aminoethyl-5-n-butylpicolinate; 10 (2'-amino-1',1'-dimethyl)ethyl-5-n-butylthiopicolinate; (2'-amino-1',1'-dimethyl)ethyl-5-n-butylpicolinate; (2'-amino-1'-methyl)ethyl-5-n-butylthiopicolinate; (2'-amino-1'-methyl)ethyl-5-n-butylpicolinate; 15 3'-aminopropyl-5-n-butylthiopicolinate; 3'-aminopropyl-5-n-butylpicolinate; (2'-amino-2'-methyl)propyl-5-n-butylthiopicolinate; (2'-amino-2'-methyl)propyl-5-n-butylpicolinate; (3'-amino-1',1'-dimethyl)propyl-5-n-butylthiopicolinate; (3'-amino-1',1'-dimethyl)propyl-5-n-butylpicolinate; 20 (3'-amino-2',2'-dimethyl)propyl-5-n-butylthiopicolinate; (3'-amino-2',2'-dimethyl)propyl-5-n-butylpicolinate; 2'-aminopropyl-5-n-butylthiopicolinate; 2'-aminopropyl-5-n-butylpicolinate; 4'-aminobutyl-5-n-butylthiopicolinate; 25 4'-amino-3'-methylbutyl-5-n-butylthiopicolinate; (3'-amino-3'-methylbutyl-5-n-butylthiopicolinate; and (3'-amino-3'-methylbutyl-5-n-butylpicolinate.

56. Conjugate of Claim 47 wherein said inhibitor compound is of the formula



wherein each of R⁸⁶, R⁸⁷ and R⁹⁰ through R⁹³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R⁸⁶ and R⁸⁷ together may form oxo or thio; wherein r is a number selected from zero through six, inclusive; wherein each of R⁸⁸ and R⁸⁹ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl.

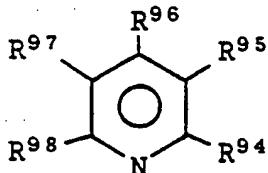
57. Conjugate of Claim 56 wherein each of R⁸⁶, R⁸⁷ and R⁹⁰ through R⁹³ is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; wherein r is a number selected from zero through four, inclusive; wherein each of R⁸⁸ and R⁸⁹ is independently selected from hydrido, alkyl, amino, monoalkylamino, dialkylamino, phenyl and phenalkyl.

58. Conjugate of Claim 57 wherein each of R⁸⁶, R⁸⁷ and R⁹⁰ through R⁹³ is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein
5 r is a number selected from zero through three, inclusive; and wherein each of R⁸⁸ and R⁸⁹ is selected from hydrido, alkyl, amino and monoalkylamino.

59. Conjugate of Claim 58 wherein each of R⁹⁰ through R⁹³ is independently selected from hydrido and alkyl; wherein each of R⁸⁶ and R⁸⁷ is hydrido; wherein r is selected from zero, one and two; wherein R⁸⁸ is selected from hydrido, alkyl and amino; and wherein R⁸⁹ is selected from hydrido and alkyl.
10

15 60. Conjugate of Claim 59 wherein said inhibitor compound is 5-n-butylpicolinic acid hydrazide.

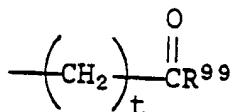
61. Conjugate of Claim 3 wherein said dopamine-β-hydroxylase inhibitor compound is of the formula
20



25 wherein each of R⁹⁴ through R⁹⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, aryloxy, alkoxy, alkylthio, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino,
30 dialkylamino, amido, alkylamido, hydroxyamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl,

thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, formoyl and alkoxy carbonyl; with the proviso that at least one of R⁹⁴ through R⁹⁸ is

5



wherein R⁹⁹ is selected from hydrido, alkyl, hydroxy, alkoxy, alkylthio, phenyl, phenoxy, benzyl, benzyloxy,

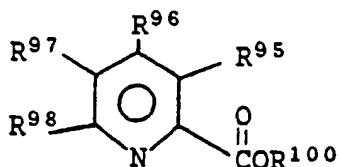
10

-OR¹⁰⁰ and -N(R¹⁰¹)₂, wherein R¹⁰⁰ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenyl and benzyl and each of R¹⁰¹ and R¹⁰² is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxy carbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein t is a number selected from zero through four, inclusive; or a pharmaceutically-acceptable salt thereof.

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62. Conjugate of Claim 61 wherein said inhibitor compound is of the formula

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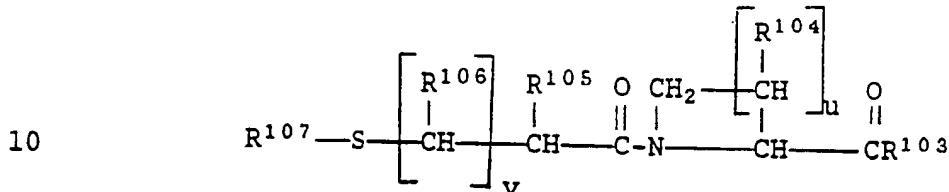
wherein each of R⁹⁵ through R⁹⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, phenyl, benzyl, alkoxy, phenoxy, benzyloxy, alkoxyalkyl, hydroxyalkyl, halo, cyano, amino,

monoalkylamino, dialkylamino, amido, alkylamido, hydroxyamino, carboxyl, carboxyalkyl, alkanoyl, cyanoamino, carboxyl, thiocarbamoyl, aminomethyl, nitro, formoyl, formyl and alkoxycarbonyl; and
5 wherein R¹⁰⁰ is selected from hydrido, alkyl, phenyl and benzyl.

63. Conjugate of Claim 62 wherein said inhibitor compound is selected from
5-n-butylicolic acid;
10 5-ethylpicolinic acid;
picolinic acid;
5-nitropicolinic acid;
5-aminopicolinic acid;
5-N-acetylaminopicolinic acid;
15 5-N-propionylaminopicolinic acid;
5-N-hydroxyaminopicolinic acid;
5-iodopicolinic acid;
5-bromopicolinic acid;
5-chloropicolinic acid;
20 5-hydroxypicolinic acid
5-methoxypicolinic acid;
5-N-propoxypicolinic acid;
5-N-butoxypicolinic acid;
5-cyanopicolinic acid;
25 5-carboxylicolic acid;
5-n-butyl-4-nitropicolinic acid;
5-n-butyl-4-methoxypicolinic acid;
5-n-butyl-4-ethoxypicolinic acid;
5-n-butyl-4-aminopicolinic acid;
30 5-n-butyl-4-hydroxyaminopicolinic acid; and
5-n-butyl-4-methylpicolinic acid.

64. Conjugate of Claim 63 wherein said inhibitor compound is 5-n-butylicolic acid.

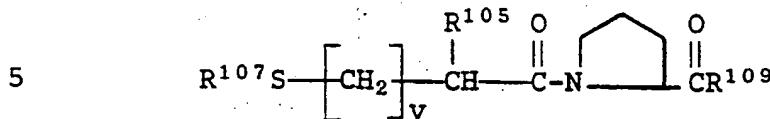
65. Conjugate of Claim 3 wherein said dopamine- β -hydroxylase inhibitor compound is of the formula



wherein R^{103} is hydrido, hydroxy, alkyl, amino and alkoxy; wherein R^{104} is selected from hydrido, hydroxy and alkyl; wherein each of R^{105} and R^{106} is independently selected from hydrido, alkyl and phenalkyl; wherein R^{107} is selected from hydrido and

25 66. Conjugate of Claim 65 wherein R^{103} is selected from hydroxy and lower alkoxy; wherein R^{104} is hydrido; wherein R^{105} is selected from hydrido and lower alkyl; wherein R^{106} is hydrido; wherein R^{107} is selected from hydrido and

67. Conjugate of Claim 66 wherein said inhibitor compound is of the formula



wherein R^{109} is selected from hydroxy and lower alkyl;
wherein R^{105} is selected from hydrido and lower alkyl;
wherein R^{107} is selected from hydrido and

10 O
 ||
 $R^{108}C-$ with R^{108} selected from lower alkyl and phenyl
and v is a number from zero to two, inclusive.

15 68. Conjugate of Claim 67 wherein R^{109} is hydroxy; wherein R^{105} is hydrido or methyl; wherein R^{107} is hydrido or acetyl; and wherein n is a number from zero to two, inclusive.

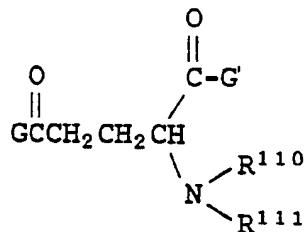
69. Conjugate of Claim 68 wherein said inhibitor compound is 1-(3-mercaptopro-2-methyl-1-oxopropyl)-L-proline.

70. Conjugate of Claim 2 wherein said precursor compound providing the second residue has a reactable acid moiety.

71. Conjugate of Claim 70 wherein said second residue precursor compound of said conjugate is selected from a class of glutamic acid derivatives of the formula

5

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wherein each of R^{110} and R^{111} may be independently selected from hydrido, alkylcarbonyl, alkoxy carbonyl, 15 alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-\text{OR}^{112}$, $-\text{SR}^{113}$ and $>\text{NR}^{114}$ with each of R^{112} , R^{113} and R^{114} independently selected from hydrido and alkyl; with the proviso that said glutamic acid is selected such 20 that formation of the cleavable amide bond occurs at the gamma-position carbon of said gamma-glutamic acid residue.

72. Conjugate of Claim 71 wherein said second residue precursor compound of said conjugate is the glutamic acid derivative gamma-glutamic acid.

73. Conjugate of Claim 72 wherein R^{110} is hydrido, and R^{111} is selected from

25

30

$\begin{array}{c} \text{O} \\ || \\ -\text{CR}^{115} \end{array}$ wherein R^{115} is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

74. Conjugate of Claim 73 wherein said second residue precursor compound of said conjugate is the glutamic acid derivative is N-acetyl- γ -glutamic acid.

5 75. Conjugate of Claim 3 which comprises a first residue provided by a dopamine- β -hydroxylase inhibitor compound and a second residue provided by a gamma glutamic acid derivative.

10 76. Conjugate of Claim 75 wherein said dopamine- β -hydroxylase inhibitor is fusaric acid or fusaric acid hydrazide and said gamma glutamic acid derivative is N-acetyl- γ -glutamic acid.

77. Conjugate of Claim 76 which is N-acetyl- γ -glutamyl fusaric acid hydrazide.

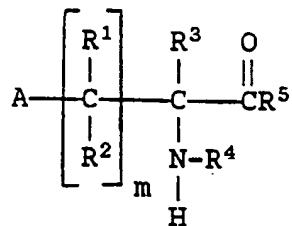
15 78. A pharmaceutical composition comprising one or more pharmaceutically-acceptable carriers or diluents and a therapeutically-effective amount of a conjugate, said conjugate comprising a first residue and a second residue, said first and 20 second residues connected together by a cleavable bond, wherein said first residue is derived from an inhibitor compound capable of inhibiting biosynthesis of an adrenergic neurotransmitter, and wherein said second residue is capable of being cleaved from the 25 first residue by an enzyme located predominantly in the kidney.

30 79. The composition of Claim 78 wherein said first and second residues are provided by precursor compounds wherein the precursor compound of one of said first and second residues has a reactable carboxylic acid moiety and the precursor of the other of said first and second residues has a reactable

amino moiety or a moiety convertible to a reactable amino moiety, whereby a cleavable bond may be formed between said carboxylic acid moiety and said amino moiety.

5 80. The composition of Claim 79 wherein
said inhibitor compound providing said first residue
is selected from tyrosine hydroxylase inhibitor
compounds, dopa-decarboxylase inhibitor compounds,
dopamine- β -hydroxylase inhibitor compounds, and mimics
10 of said inhibitor compounds.

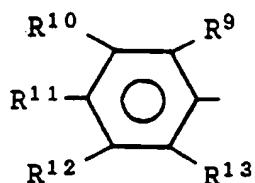
81. The composition of Claim 80 wherein
said tyrosine hydroxylase inhibitor compound is of the
formula



wherein each of R¹ through R³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxy-
alkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl;
wherein R⁴ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alcoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein R⁵ is selected from -OR⁶ and

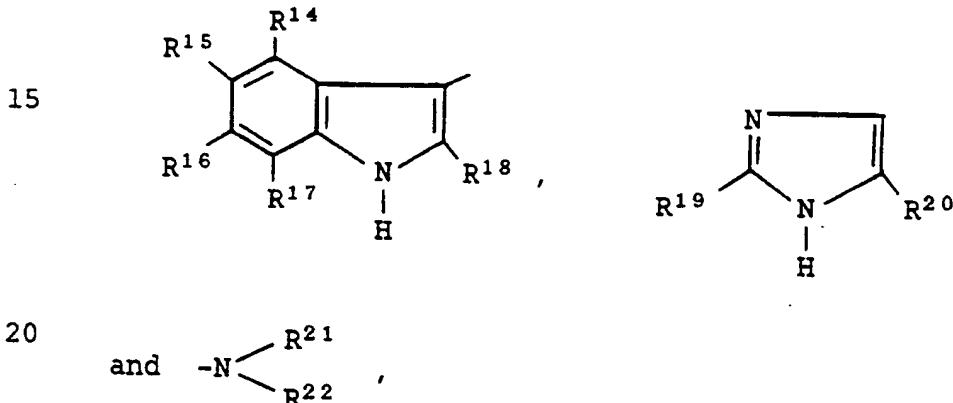
35 $\begin{array}{c} \text{R}^7 \\ | \\ -\text{N}- \\ | \\ \text{R}^8 \end{array}$, wherein R⁶ is selected from hydrido, alkyl,

- cycloalkyl, cycloalkylalkyl, aralkyl and aryl, and
wherein each of R⁷ and R⁸ is independently selected
from hydrido, alkyl, cycloalkyl, hydroxyalkyl,
haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl,
5 aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino,
cyanoamino, monoalkylamino, dialkylamino, alkyl-
sulfinyl, alkylsulfonyl, arylsulfinyl and aryl-
sulfonyl; aralkyl; wherein m is a number selected
from zero through six;
- 10 wherein A is a phenyl ring of the formula



- wherein each of R⁹ through R¹³ is independently
15 selected from hydrido, hydroxy, alkyl, cycloalkyl,
cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy,
alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano,
amino, monoalkylamino, dialkylamino, carboxyl,
carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl,
20 alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl,
aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy,
carboxyalkoxy, formyl and a substituted or unsub-
stituted 5- or 6-membered heterocyclic ring selected
from the group consisting of pyrrol-1-yl, 2-carboxy-
25 pyrrol-1-yl, imidazol-2-ylamino, indol-1-yl, carbozol-
9-yl, 4,5-dihydro-4-hydroxy-4-trifluoromethylthiazol-
3-yl, 4-trifluoromethylthiazol-2-yl, imidazol-2-yl
and 4,5-dihydroimidazol-2-yl; wherein any two of the
R⁹ through R¹³ groups may be taken together to form a
30 benzoheterocyclic ring selected from the group consist-
ing of indolin-5-yl, 1-(N-benzoylcarbamimidoyl)indolin-
5-yl, 1-carbamimidoylindolin-5-yl, 1H-2-oxindol-5-yl,
insol-5-yl, 2-mercaptopbenzimidazol-5(6)-yl,

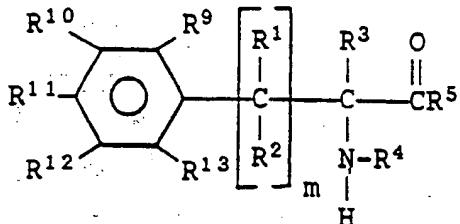
2-aminobenzimidazol-5-(6)-yl, 2-methanesulfonamido-benzimidazol-5(6)-yl, 1H-benzoxanol-2-on-6-yl, 2-aminobenzothiazol-6-yl, 2-amino-4-mercaptopbenzothiazol-6-yl, 2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-1,3-dimethyl-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 4-methyl-2(H)-oxoquinolin-6-yl, quinoxalin-6-yl, 2-hydroxyquinoxalin-6-yl, 2-hydroxquinoxalin-7-yl, 2,3-dihydroxyquinoxalin-6-yl and 2,3-didydro-3(4H)-oxo-1,4-benzoxazin-7-yl;
 5 10 5-hydroxy-4H-pyran-4-on-2-yl, 2-hydroxypyrid-4-yl, 2-aminopyrid-4-yl, 2-carboxypyrid-4-yl or tetrazolo-[1,5-a]pyrid-7-yl; and wherein A may be selected from



wherein each of R¹⁴ through R²⁰ is independently selected from hydrido, alkyl, hydroxy, hydroxyalkyl, alkoxy, cycloalkyl, cycloalkylalkyl, halo, haloalkyl, aryloxy, alkoxyacetyl, aryl, aralkyl, cyano, cyanoalkyl, amino, monoalkylamino and dialkylamino, wherein each of R²¹ and R²² is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxyacetyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; or a pharmaceutically-acceptable salt thereof.

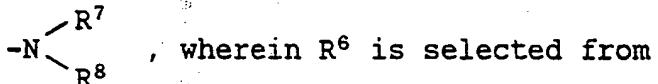
82. The composition of Claim 81 wherein said inhibitor compound is of the formula

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10 wherein each of R¹ and R² is hydrido; wherein m is one; wherein R³ is selected from alkyl, alkenyl and alkynyl; wherein R⁴ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein R⁵ is selected from OR⁶ and

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wherein R⁶ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl and phenyl, and wherein each of R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R⁹ through R¹³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxycarbonyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, pyrrol-1-yl 2-carboxypyrrrol-1-yl, imidazol-2-ylamino, indol-1-yl,

carbazol-9-yl, 4,5-dihydro-4-trifluoromethylthiazol-3-yl, 4-trifluoromethylthiazol-2-yl, imidazol-2-yl and 4,5-dihydroimidazol-2-yl, and wherein any two of the R⁹ through R¹³ groups may be taken together to form a benzoheterocyclic ring selected from the group consisting of indolin-5-yl, 1-(N-benzoylcarbamimidoyl)-indolin-5-yl, 1-carbamimidoylindolin-5-yl, 1H-2-oxindol-5-yl, indol-5-yl, 2-mercaptopbenzimidazol-5(6)-yl, 2-aminobenzimidazol-5-(6)-yl, 2-methanesulfonamido-benzimidazol-5(6)-yl, 1H-benzoxanol-2-on-6-yl, 2-amino-benzothiazol-6-yl, 2-amino-4-mercaptopbenzothiazol-6-yl, 2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-1,3-dimethyl-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 4-methyl-2(H)-oxoquinolin-6-yl, quinoxalin-6-yl, 2-hydroxyquinoxalin-6-yl, 2-hydroxquinoxalin-7-yl, 2,3-dihydroxyquinoxalin-6-yl and 2,3-dihydro-3(4H)-oxo-1,4-benzoxazin-7-yl; wherein R⁵ is -CH=CH₂ or -C≡CH; wherein R⁶ is selected from hydrido, alkyl, hydroxy, hydroxyalkyl, alkoxy, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino; and wherein each of R⁷ and R⁸ independently is selected from hydrido, alkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; or a pharmaceutically-acceptable salt thereof.

83. The composition of Claim 82 wherein said inhibitor compound is selected from the group consisting of
4-cyanoamino- α -methylphenylalanine;
30 3-carboxy- α -methylphenylalanine;
3-cyano- α -methylphenylalanine methyl ester;
 α -methyl-4-thiocarbamoylphenylalanine methyl ester;
4-(aminomethyl)- α -methylphenylalanine;
4-guanidino- α -methylphenylalanine;
35 3-hydroxy-4-methanesulfonamido- α -methylphenylalanine;
3-hydroxy-4-nitro- α -methylphenylalanine;

4-amino-3-methanesulfonyloxy- α -methylphenylalanine;
3-carboxymethoxy-4-nitro- α -methylphenylalanine;
 α -methyl-4-amino-3-nitrophenylalanine;
3,4-diamino- α -methylphenylalanine;
5 α -methyl-4-(pyrrol-1-yl)phenylalanine;
4-(2-aminoimidazol-1-yl)- α -methylphenylalanine;
4-(imidazol-2-ylamino)- α -methylphenylalanine;
4-(4,5-dihydro-4-hydroxy-4-trifluoromethyl-thiazol-2-yl)-
 α -methylphenylalanine methyl ester;
10 α -methyl-4-(4-trifluoromethylthiazol-2-yl)phenylalanine;
 α -methyl-3-(4-trifluoromethylthiazol-2-yl)-phenyl-
alanine;
4-(imidazol-2-yl)- α -methylphenylalanine;
4-(4,5-dihydroimidazol-2-yl)- α -methylphenylalanine;
15 3-(imidazol-2-yl)- α -methylphenylalanine;
3-(4,5-dihydroimidazol-2-yl)- α -methylphenylalanine;
4-(imidazol-2-yl)phenylalanine;
4,5-dihydroimidazol-2-yl)phenylalanine;
3-(imidazol-2-yl)phenylalanine;
20 3-(2,3-dihydro-1H-indol-4-yl)- α -methylalanine;
 α -methyl-3-(1H-2-oxindol-5-yl)alanine;
3-[1-(N-benzoylcarbamimidoyl)-2,3-dihydro-1H-
indol-5-yl)]- α -methylalanine;
3-(1-carbamimidoyl-2,3-dihydro-1H-indol-5-yl- α -
25 methylalanine;
3-(1H-indol-5-yl)- α -methylalanine;
3-(benzimidazol-2-thione-5-yl)- α -methylalanine;
3-(2-aminobenzimidazol-5-yl-2-methylalanine;
2-methyl-3-(benzoxazol-2-on-6-yl)alanine;
30 3-(2-aminobenzothiazol-6-yl)-2-methylalanine;
3-(2-amino-4-mercaptopbenzothiazol-6-yl)-2-
methylalanine;
3-(2-aminobenzothiazol-6-yl)alanine;
2-methyl-3-(2,1,3-benzothiadiazol-5-yl)alanine;
35 3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)-2-
methylalanine-2,2-dioxide;

- 3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)-2-methylalanine-2,2-dioxide methyl ester;
- 3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)alanine 2,2-dioxide;
- 5 3-(1,3-dihydro-1,3-dimethylbenzo-2,1,3-thiadiazol-5-yl)-2-methylalanine 2,2-dioxide;
- α -methyl-3-[4-methyl-2(1H)-oxoquinolin-6-yl]alanine;
- 3-[4-methyl-2(1H)-oxoquinolin-6-yl]alanine;
- 2-methyl-3-(quinoxalin-6-yl)alanine;
- 10 2-methyl-3-(2-hydroxyquinoxalin-6-yl)alanine;
- 2-methyl-3-(2-hydroxyquinoxalin-7-yl)alanine;
- 3-(2,3-dihydroxyquinoxalin-6-yl)-2-methylalanine;
- 3-(quinoxalin-6-yl)alanine;
- 3-(2,3-dihydroxyquinoxalin-6-yl)alanine;
- 15 3-(1,4-benzoxazin-3-one-6-yl)-2-methylalanine;
- 3-(1,4-benzoxazin-3-one-7-yl)alanine;
- 3-(5-hydroxy-4H-pyran-4-on-2-yl)-2-methylalanine;
- 3-(2-hydroxy-4-pyridyl)-2-methylalanine;
- 3-(2-carboxy-4-pyridyl)-2-methylamine;
- 20 α -methyl-4-(pyrrol-1-yl)phenylalanine;
- α -ethyl-4-(pyrrol-1-yl)phenylalanine;
- α -propyl-4-(pyrrol-1-yl)phenylalanine;
- 4-[2-(carboxy)pyrrol-1-yl]phenylalanine;
- α -methyl-4-(pyrrol-1-yl)phenylalanine;
- 25 3-hydroxy- α -methyl-4-(pyrrol-1-yl)phenylalanine;
- 3-methoxy- α -methyl-4-(pyrrol-1-yl)phenylalanine;
- 4-methoxy- α -methyl-3-(pyrrol-1-yl)phenylalanine;
- 4-(indol-1-yl)- α -methylphenylalanine;
- 4-(carbazol-9-yl)- α -methylphenylalanine;
- 30 2-methyl-3-(2-methanesulfonylamidobenzimidazol-5-yl)alanine;
- 2-methyl-3-(2-amino-4-pyridyl)alanine;
- 2-methyl-3[tetrazolo-(1,5)- α -pyrid-7-yl]alanine;
- D,L- α -methyl- β -(4-hydroxy-3-methyl)phenylalanine;
- 35 D,L- α -methyl- β -(4-hydroxy-3-phenyl)phenylalanine;
- D,L- α -methyl- β -(4-hydroxy-3-benzyl)phenylalanine;

- D,L- α -methyl- β -(4-methoxy-3-cyclohexyl)phenylalanine;
 α , β , β -trimethyl- β -(3,4-dihydroxyphenyl)alanine;
 α , β , β -trimethyl- β -(4-hydroxyphenyl)alanine;
- 5 N-methyl- α , β , β -trimethyl- β -(3,4-dihydroxyphenyl)-alanine;
D,L- α , β , β -trimethyl- β -(3,4-dihydroxyphenyl)alanine;
 α , β , β -trimethyl- β -(3,4-dimethoxyphenyl)alanine;
L- α -methyl- β -3,4-dihydroxyphenylalanine;
- 10 L- α -ethyl- β -3,4-dihydroxyphenylalanine;
L- α -propyl- β -3,4-dihydroxyphenylalanine;
L- α -butyl- β -3,4-dihydroxyphenylalanine;
L- α -methyl- β -2,3-dihydroxyphenylalanine;
L- α -ethyl- β -2,3-dihydroxyphenylalanine;
- 15 L- α -propyl- β -2,3-dihydroxyphenylalanine;
L- α -butyl- β -2,3-dihydroxyphenylalanine;
L- α -methyl-4-chloro-2,3-dihydroxyphenylalanine;
L- α -ethyl-4-chloro-2,3-dihydroxyphenylalanine;
L- α -propyl-4-chloro-2,3-dihydroxyphenylalanine;
- 20 20 L- α -butyl-4-chloro-2,3-dihydroxyphenylalanine;
L- α -ethyl- β -4-methyl-2,3-dihydroxyphenylalanine;
L- α -methyl- β -4-methyl-2,3-dihydroxyphenylalanine;
L- α -propyl- β -4-methyl-2,3-dihydroxyphenylalanine;
L- α -butyl- β -4-methyl-2,3-dihydroxyphenylalanine;
- 25 25 L- α -methyl- β -4-fluoro-2,3-dihydroxyphenylalanine;
L- α -ethyl- β -4-fluoro-2,3-dihydroxyphenylalanine;
L- α -propyl- β -4-fluoro-2,3-dihydroxyphenylalanine;
L- α -butyl- β -4-fluoro-2,3-dihydroxyphenylalanine;
L- α -methyl- β -4-trifluoromethyl-2,3-dihydroxyphenyl-
- 30 30 alanine
L- α -ethyl- β -4-trifluoromethyl-2,3-dihydroxyphenylalanine
L- α -propyl- β -4-trifluoromethyl-2,3-dihydroxyphenylalanine
- 35 35 L- α -butyl- β -4-trifluoromethyl-2,3-dihydroxyphenylalanine

- L- α -methyl- β -3,5-dihydroxyphenylalanine;
L- α -ethyl- β -3,5-dihydroxyphenylalanine;
L- α -propyl- β -3,5-dihydroxyphenylalanine;
L- α -butyl- β -3,5-dihydroxyphenylalanine;
5 L- α -methyl- β -4-chloro-3,5-dihydroxyphenylalanine;
L- α -ethyl- β -4-chloro-3,5-dihydroxyphenylalanine;
L- α -propyl- β -4-chloro-3,5-dihydroxyphenylalanine;
L- α -butyl- β -4-chloro-3,5-dihydroxyphenylalanine;
L- α -methyl- β -4-fluoro-3,5-dihydroxyphenylalanine;
10 L- α -ethyl- β -4-fluoro-3,5-dihydroxyphenylalanine;
L- α -propyl- β -4-fluoro-3,5-dihydroxyphenylalanine;
L- α -butyl- β -4-fluoro-3,5-dihydroxyphenylalanine;
L- α -methyl- β -4-trifluoromethyl-3,5-dihydroxyphenyl-
alanine;
15 L- α -ethyl- β -4-trifluoromethyl-3,5-dihydroxyphenyl-
alanine;
L- α -propyl- β -4-trifluoromethyl-3,5-dihydroxyphenyl-
alanine;
L- α -butyl- β -4-trifluoromethyl-3,5-dihydroxyphenyl-
20 alanine;
L- α -methyl-2,5-dihydroxyphenylalanine;
L- α -ethyl-2,5-dihydroxyphenylalanine;
L- α -propyl-2,5-dihydroxyphenylalanine;
L- α -butyl-2,5-dihydroxyphenylalanine;
25 L- α -methyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -ethyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -propyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -butyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -methyl- β -4-chloro-2,5-dihydroxyphenylalanine;
30 L- α -ethyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -propyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -butyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -methyl- β -methyl-2,5-dihydroxyphenylalanine;
L- α -ethyl- β -methyl-2,5-dihydroxyphenylalanine;
35 L- α -propyl- β -methyl-2,5-dihydroxyphenylalanine;
L- α -butyl- β -methyl-2,5-dihydroxyphenylalanine;

- L- α -methyl- β -4-trifluoromethyl-2,5-dihydroxyphenylalanine;
L- α -ethyl- β -4-trifluoromethyl-2,5-dihydroxyphenylalanine;
5 L- α -propyl- β -4-trifluoromethyl-2,5-dihydroxyphenylalanine;
L- α -butyl- β -4-trifluoromethyl-2,5-dihydroxyphenylalanine;
L- α -methyl- β -3,4,5-trihydroxyphenylalanine;
10 L- α -ethyl- β -3,4,5-trihydroxyphenylalanine;
L- α -propyl- β -3,4,5-trihydroxyphenylalanine;
L- α -butyl- β -3,4,5-trihydroxyphenylalanine;
L- α -methyl- β -2,3,4-trihydroxyphenylalanine;
15 L- α -ethyl- β -2,3,4-trihydroxyphenylalanine;
L- α -propyl- β -2,3,4-trihydroxyphenylalanine;
L- α -butyl- β -2,3,4-trihydroxyphenylalanine;
L- α -methyl- β -2,4,5-trihydroxyphenylalanine;
20 L- α -ethyl- β -2,4,5-trihydroxyphenylalanine;
L-phenylalanine;
D,L- α -methylphenylalanine;
D,L-3-iodophenylalanine;
D,L-3-iodo- α -methylphenylalanine;
25 3-iodotyrosine;
3,5-diiodotyrosine;
L- α -methylphenylalanine;
D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)alanine;
D,L- α -methyl- β -(4-methoxy-3-benzylphenyl)alanine;
30 D,L- α -methyl- β -(4-hydroxy-3-benzylphenyl)alanine;
D,L- α -methyl- β -(4-methoxy-3-cyclohexylphenyl)alanine;
D,L- α -methyl- β -(4-hydroxy-3-cyclohexylphenyl)alanine;
D,L- α -methyl- β -(4-methoxy-3-methylphenyl)alanine;
35 D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)alanine;
N,O-dibenzoyloxycarbonyl-D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)alanine;

- N,O-dibenzylloxycarbonyl-D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)alanine amide;
D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)-alanine amide;
- 5 N,O-diacetyl-D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)alanine;
D,L-N-acetyl- α -methyl- β -(4-hydroxy-3-methylphenyl)-alanine;
L-3,4-dihydroxy- α -methylphenylalanine;
10 L-4-hydroxy-3-methoxy- α -methylphenylalanine;
L-3,4-methylene-dioxy- α -methylphenylalanine;
2-vinyl-2-amino-3-(2-methoxyphenyl)propionic acid;
2-vinyl-2-amino-3-(2,5-dimethoxyphenyl)propionic acid;
2-vinyl-2-amino-3-(2-imidazolyl)propionic acid;
15 2-vinyl-2-amino-3-(2-methoxyphenyl)propionic acid ethyl ester;
 α -methyl- β -(2,5-dimethoxyphenyl)alanine;
 α -methyl- β -(2,5-dihydroxyphenyl)alanine;
 α -ethyl- β -(2,5-dimethoxyphenyl)alanine;
20 α -ethyl- β -(2,5-dihydroxyphenyl)alanine;
 α -methyl- β -(2,4-dimethoxyphenyl)alanine;
 α -methyl- β -(2,4-dihydroxyphenyl)alanine;
 α -ethyl- β -(2,4-dimethoxyphenyl)alanine;
 α -ethyl- β -(2,4-dihydroxyphenyl)alanine;
25 α -methyl- β -(2,5-dimethoxyphenyl)alanine ethyl ester;
2-ethynyl-2-amino-3-(3-indolyl)propionic acid;
2-ethynyl-2,3-(2-methoxyphenyl)propionic acid;
2-ethynyl-2,3-(5-hydroxyindol-3-yl)propionic acid;
- 30 2-ethynyl-2-amino-3-(2,5-dimethoxyphenyl)propionic acid;
2-ethynyl-2-amino-3-(2-imidazolyl)propionic acid;
2-ethynyl-2-amino-3-(2-methoxyphenyl)propionic acid ethyl ester;
- 35 3-carbomethoxy-3-(4-benzylloxybenzyl)-3-aminoprop-1-yne;
 α -ethynyltyrosine hydrochloride;
 α -ethynyltyrosine;
 α -ethynyl-m-tyrosine;

α -ethynyl- β -(2-methoxyphenyl)alanine;
 α -ethynyl- β -(2,5-dimethoxyphenyl)alanine; and
 α -ethynylhistidine.

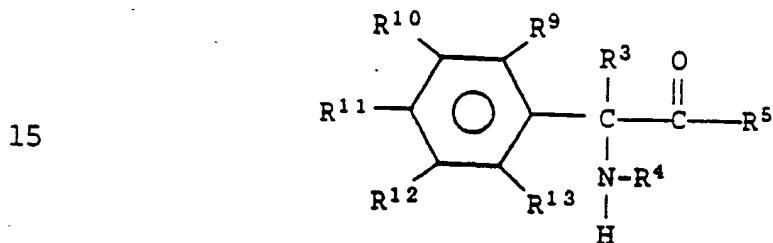
84. The composition of Claim 82 wherein at least one of R¹⁰, R¹¹ and R¹² is selected from hydroxy, alkoxy, aryloxy, aralkoxy and alkoxycarbonyl.

85. The composition of Claim 84 wherein said inhibitor compound is selected from the group consisting of

- 10 α -methyl-3-(pyrrol-1-yl)tyrosine;
 α -methyl-3-(4-trifluoromethylthiazol-2-yl)tyrosine;
 3-(imidazol-2-yl)- α -methyltyrosine;
 L- α -methyl-m-tyrosine;
 L- α -ethyl-m-tyrosine;
15 L- α -propyl-m-tyrosine;
 L- α -butyl-m-tyrosine;
 L- α -methyl-p-chloro-m-tyrosine;
 L- α -ethyl-p-chloro-m-tyrosine;
 L- α -butyl-p-chloro-m-tyrosine;
20 L- α -methyl-p-bromo-m-tyrosine;
 L- α -ethyl-p-bromo-m-tyrosine;
 L- α -butyl-p-bromo-m-tyrosine;
 L- α -methyl-p-fluoro-m-tyrosine;
 L- α -methyl-p-iodo-m-tyrosine;
25 L- α -ethyl-p-iodo-m-tyrosine;
 L- α -methyl-p-methyl-m-tyrosine;
 L- α -methyl-p-ethyl-m-tyrosine;
 L- α -ethyl-p-ethyl-m-tyrosine;
 L- α -ethyl-p-methyl-m-tyrosine;
30 L- α -methyl-p-butyl-m-tyrosine;
 L- α -methyl-p-trifluoromethyl-m-tyrosine;
 L-3-iodotyrosine;
 L-3-chlorotyrosine;
 L-3,5-diiodotyrosine;

L- α -methyltyrosine;
D,L- α -methyltyrosine;
D,L-3-iodo- α -methyltyrosine;
L-3-bromo- α -methyltyrosine;
5 D,L-3-bromo- α -methyltyrosine;
L-3-chloro- α -methyltyrosine;
D,L-3-chloro- α -methyltyrosine; and
2-vinyl-2-amino-3-(4-hydroxyphenyl)propionic acid.

10 86. The composition of Claim 81 wherein
said inhibitor compound is of the formula



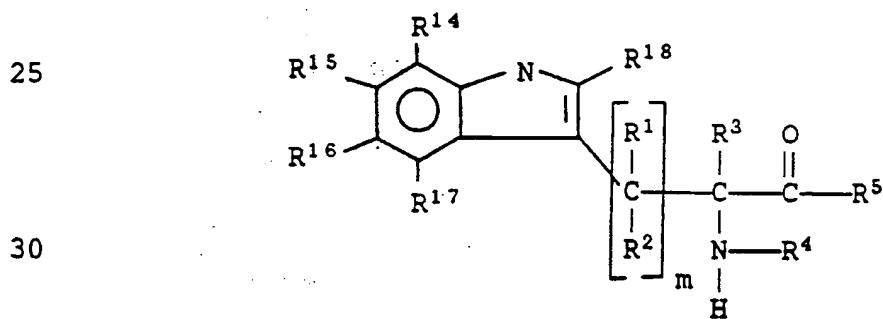
wherein R³ is selected from alkyl, alkenyl and alkynyl;
wherein R⁴ is selected from hydrido, alkyl, cycloalkyl,
hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl,
aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl,
amino, cyanoamino, monoalkylamino, dialkylamino,
alkylsulfinyl, alkylsulfonyl, arylsulfinyl and
arylsulfonyl; wherein m is a number selected from
20 zero through five, inclusive; wherein R⁵ is selected
from OR⁶ and
R⁷
-N<
R⁸, wherein R⁶ is selected from
25 hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl
and phenyl, and wherein each of R⁷ and R⁸ is independ-
ently selected from hydrido, alkyl, cycloalkyl,
hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl,
aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl,
30

amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R⁹ through R¹³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, 5 cycloalkylalkyl, aralkyl, aryl, alkoxycarbonyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, alkoxycarbonyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

10 87. The composition of Claim 86 wherein at least one of R¹⁰, R¹¹ and R¹² is selected from hydroxy, alkoxy, aryloxy, aralkoxy and alkoxycarbonyl.

15 88. The composition of Claim 87 wherein said inhibitor compound is selected from the group consisting of methyl(+)-2-(4-hydroxyphenyl)glycinate; isopropyl and 3-methyl butyl esters of (+)-2-(4-hydroxyphenyl)glycine; (+)-2-(4-hydroxyphenyl)glycine; (-)-2-(4-hydroxyphenyl)glycine; (+)-2-(4-methoxyphenyl)-glycine; and (+)-2-(4-hydroxyphenyl)glycinamide.

20 89. The composition of Claim 81 wherein said inhibitor compound is of the formula



wherein each of R¹ and R² is hydrido; wherein R³ is selected from alkyl, alkenyl and alkynyl; wherein R⁴ is selected from hydrido, alkyl, cycloalkyl, hydroxy-alkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl,
5 aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein m is a number selected from zero through five, inclusive; wherein each of R¹⁴ through
10 R¹⁷ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cyclo-alkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl,
15 alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy and formyl.

90. The composition of Claim 89 wherein said inhibitor compound is selected from the group consisting of L- α -methyltryptophan;
20 D,L-5-methyltryptophan;
D,L-5-chlorotryptophan;
D,L-5-bromotryptophan;
D,L-5-iodotryptophan;
25 L-5-hydroxytryptophan;
D,L-5-hydroxy- α -methyltryptophan;
 α -Ethynyltryptophan;
5-Methoxymethoxy- α -ethynyltryptophan; and
5-Hydroxy- α -ethynyltryptophan.

30 91. The composition of Claim 81 wherein A is

35
$$\begin{array}{c} \text{R}^{21} \\ | \\ -\text{N}- \\ | \\ \text{R}^{22} \end{array}$$
, and m is a number selected from zero to three, inclusive.

92. The composition of Claim 91 wherein said inhibitor compound is selected from the group consisting of 2-vinyl-2-amino-5-aminopentanoic acid and 2-ethynyl-2-amino-5-aminopentanoic acid.

5 93. The composition of Claim 81 wherein
said inhibitor compound is of the formula

10

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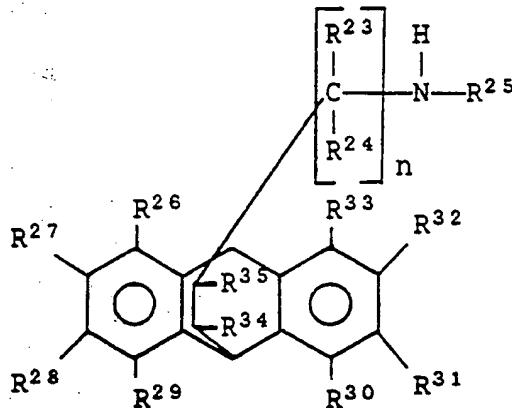
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wherein each of R²³ and R²⁴ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R²⁵ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R²⁶ through R³⁵ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl;

25

30

35

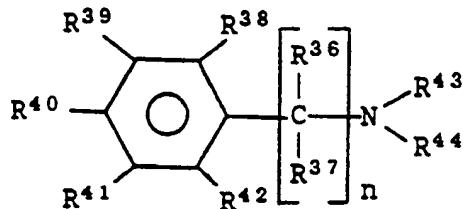


5 alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, alkoxy and formyl; wherein n is a number selected from zero to five, inclusive; or a pharmaceutically-acceptable salt thereof.

94. The composition of Claim 93 wherein said inhibitor compound is benzoctamine.

10 95. The composition of Claim 80 wherein said inhibitor compound is a dopa-decarboxylase inhibitor of the formula

15



wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy and formyl; wherein n is a whole number from zero through four; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, alkenyl, cycloalkenyl and alkynyl, with the proviso that R⁴³ and R⁴⁴ cannot

both be carboxyl at the same time, and with the further proviso that at least one of R⁴³ through R⁴⁴ is a primary or secondary amino group; or a pharmaceutically-acceptable salt thereof.

5 96. The composition of Claim 95 wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl; wherein n is a whole number from one through three; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, 10 alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl and alkanoyl.

15 97. The composition of Claim 96 wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, benzyl, phenyl, alkoxy, benzyloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, cyanoamino, cyano, aminomethyl, carboxyl, carboxyalkoxy and formyl; 20 wherein n is one or two; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, benzyl, phenyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl and alkanoyl.

98. The composition of Claim 97 wherein
each of R³⁶ through R⁴² is independently selected from
hydrido, hydroxy, alkyl, alkoxy, haloalkyl,
hydroxyalkyl, amino, monoalkylamino, carboxyl,
5 carboxyalkyl, aminomethyl, carboxyalkoxy and formyl;
wherein n is one or two; wherein each of R⁴³ and R⁴⁴
is independently selected from hydrido, alkyl,
haloalkyl, hydroxyalkyl, amino, monoalkylamino,
carboxyl and carboxyalkyl.

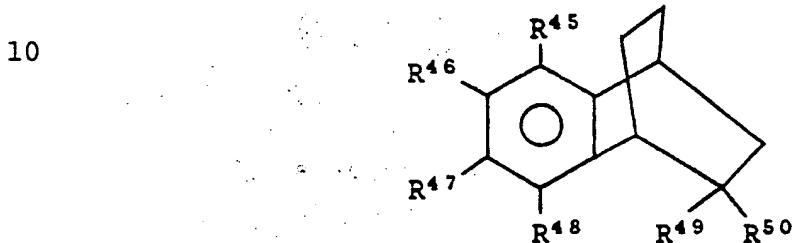
10 99. The composition of Claim 98 wherein
each of R³⁶ and R⁴² is hydrido and n is one; wherein
each of R³⁸ through R⁴² is independently selected from
hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl,
amino, monoalkylamino, carboxyl, carboxyalkyl,
15 aminomethyl, carboxyalkoxy and formyl; wherein each of
R⁴³ and R⁴⁴ is independently selected from hydrido,
alkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino,
carboxyl and carboxyalkyl.

20 100. The composition of Claim 99 wherein
said inhibitor compound is selected from
(2,3,4-trihydroxy)benzylhydrazine; 1-(D,L-seryl-2-
(2,3,4-trihydroxybenzyl)hydrazine; and
1-(3-hydroxylbenzyl)-1-methylhydrazine.

25 101. The composition of Claim 98 wherein
each of R³⁶ and R³⁷ is independently selected from
hydrido, alkyl and amino and n is two; wherein each of
R³⁸ through R⁴² is independently selected from
hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl,
amino, monoalkylamino, carboxyl, carboxyalkyl,
30 aminomethyl, carboxyalkoxy and formyl; wherein each of
R⁴³ and R⁴⁴ is independently selected from hydrido,
alkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino,
carboxyl and carboxyalkyl.

102. The composition of Claim 101 wherein
said inhibitor compound is selected from
2-hydrazino-2-methyl-3-(3,4-dihydroxyphenyl)propionic
acid; α -(monofluoromethyl)dopa; and
5 α -(difluoromethyl)dopa.

103. The composition of Claim 80 wherein
said inhibitor compound is a dopa-decarboxylase
inhibitor of the formula



15 wherein each of R^{45} through R^{48} is independently
selected from hydrido, hydroxy, alkyl, cycloalkyl,
cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy,
alkoxyalkyl, haloalkyl, hydroxyalkyl, halo,
amino, monoalkylamino, dialkylamino, carboxyl,
carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl,
20 alkynyl, cyanoamino, cyano, thiocarbamoyl,
aminomethyl, alkylsulfanamido, nitro,
alkylsulfonyloxy, carboxyalkoxy and formyl;
wherein each of R^{49} and R^{50} is independently selected
from hydrido, alkyl, cycloalkyl, cycloalkylalkyl,
25 aralkyl, aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl,
cyano, amino, monoalkylamino, dialkylamino,
carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl,
alkynyl and

30 $\begin{array}{c} \text{O} \\ || \\ -\text{CR}^{51} \end{array}$ wherein R^{51} is selected from hydroxy, alkoxy,
aryloxy, aralkoxy, amino, monoalkylamino and dialkyl-
amino; with the proviso that R^{49} and R^{50} cannot both

be carboxyl at the same time, and with the further proviso that at least one of R⁴⁵ through R⁴⁸ is a primary or secondary amino group or a carboxyl group; or a pharmaceutically-acceptable salt thereof.

5 104. The composition of Claim 103 wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, 10 monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴⁹ and R⁵⁰ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, 15 aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyalkyl and alkanoyl and

20 O
||
-CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy, phenoxy, benzyloxy, amino, monoalkylamino and dialkylamino.

25 105. The composition of Claim 104 wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, benzyl, phenyl, alkoxy, benzyloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl; wherein each 30 of R⁴⁹ and R⁵⁰ is independently selected from hydrido, alkyl, benzyl, phenyl, alkoxyalkyl,

haloalkyl, hydroxyalkyl, cyano, amino,
monoalkylamino, dialkylamino, carboxyalkyl and
alkanoyl and

5 O
 ||
 -CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy,
amino and monoalkylamino.

106. The composition of Claim 105 wherein
each of R⁴⁵ through R⁴⁸ is independently selected from
hydrido, hydroxy, alkyl, alkoxy, haloalkyl,
hydroxyalkyl, amino, monoalkylamino, carboxyl,
carboxyalkyl aminomethyl, carboxyalkoxy and formyl;
wherein each of R⁴⁹ and R⁵⁰
15 is independently selected from hydrido alkyl, amino,
monoalkylamino, carboxyalkyl and

 O
 ||
 -CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy,
amino and monoalkylamino.

107. The composition of Claim 106 wherein
each of R⁴⁵ through R⁴⁸ is independently selected from
hydrido, hydroxy, alkyl, alkoxy and hydroxyalkyl;
wherein each of R⁴⁹ and R⁵⁰ is independently selected
from alkyl, amino, monoalkylamino, and

25 O
 ||
 -CR⁵¹ wherein R⁵¹ is selected from hydroxy, methoxy,
ethoxy, propoxy, butoxy, amino, methylamino and
ethylamino.

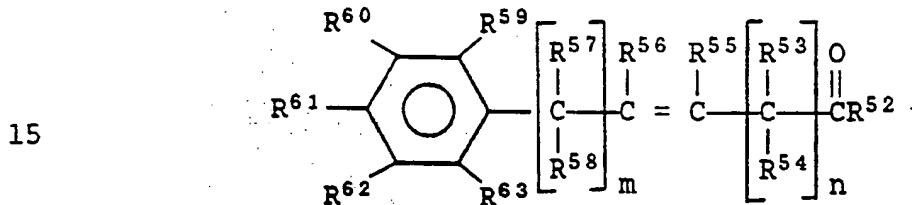
108. The composition of Claim 107 wherein
said inhibitor compound is selected from endo-2-
amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-
2-carboxylic acid; ethyl-endo-2-amino-1,2,3,

4-tetrahydro-1,4-ethano-naphthalene-2-carboxylate hydrochloride; exo-2-amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylic acid; and ethyl-exo-2-amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylate hydrochloride.

109. The composition of Claim 80 wherein said inhibitor compound is a dopa-decarboxylase inhibitor selected from 2,3-dibromo-4,4-bis (4-ethylphenyl)-2-butenoic acid; 3-bromo-4-(4-methoxyphenyl)-4-oxo-2-butenoic acid; N-(5'-phosphopyridoxyl)-L-3,4-dihydroxyphenylalanine; N-(5'-phosphopyridoxyl)-L-m-aminotyrosine; D,L-β-(3,4-dihydroxyphenyl)lactate; D,L-β-(5-hydroxyindolyl-3)lactate;
- 15 2,4-dihydroxy-5-(1-oxo-2-propenyl)benzoic acid; 2,4-dimethoxy-5-[1-oxo-3-(2,3,4-trimethoxyphenyl-2-propenyl]benzoic acid; 2,4-dihydroxy-5-[1-oxo-3-(2-thienyl)-2-propenyl]benzoic acid;
- 20 2,4-dihydroxy-5-[3-(4-hydroxyphenyl)-1-oxo-2-propenyl]benzoic acid; 5-[3-(4-chlorophenyl)-1-oxo-2-propenyl]-2,4-dihydroxybenzoic acid;
- 25 2,4-dihydroxy-5-(1-oxo-3-phenyl-2-propenyl)benzoic acid; 2,4-dimethoxy-5-[1-oxo-3-(4-pyridinyl)-2-propenyl]benzoic acid;
- 30 5-[3-(3,4-dimethoxyphenyl)-1-oxo-2-propenyl]-2,4-dimethoxybenzoic acid; 2,4-dimethoxy-5-(1-oxo-3-phenyl-2-propenyl)benzoic acid; 5-[3-(2-furanyl)-1-oxo-2-propenyl]-2,4-dimethoxybenzoic acid; 2,4-dimethoxy-5-[1-oxo-3-(2-thienyl)-2-propenyl]

benzoic acid;
 2,4-dimethoxy-5-[3-(4-methoxyphenyl)-1-oxo-2-propenyl]benzoic acid;
 5-[3-(4-chlorophenyl)-1-oxo-2-propenyl]-2,4-dimethoxy
 5 benzoic acid; and
 5-[3-[4-(dimethylamino)phenyl]-1-oxo-2-propenyl]-2,4
 dimethoxy benzoic acid.

110. The composition of Claim 80 wherein
 said inhibitor compound is a dopa-decarboxylase
 10 inhibitor of the formula



wherein R⁵² is selected from hydrido, OR⁶⁴ and
 20 -N(R⁶⁵)R⁶⁶, wherein R⁶⁴ is selected from
 hydrido, alkyl, cycloalkyl, cycloalkylalkyl,
 phenalkyl and phenyl, and wherein each of R⁶⁵ and R⁶⁶
 25 is independently selected from hydrido, alkyl,
 alkanoyl, amino, monoalkylamino, dialkylamino, phenyl
 and phenalkyl; wherein each of R⁵³, R⁵⁴ and R⁵⁷
 through R⁶³ is independently selected from hydrido,
 hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl,
 aryl, alkoxycarbonyl, hydroxyalkyl, halo, cyano,
 30 amino, monoalkylamino, dialkylamino, carboxyl,
 carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and
 alkynyl; wherein each of R⁵⁵ and R⁵⁶ is independently
 selected from hydrido, alkyl, cycloalkyl,
 cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl,

haloalkyl, hydroxyalkyl and carboxyalkyl; wherein each of m and n is a number independently selected from zero through six, inclusive; or a pharmaceutically-acceptable salt thereof.

5 111. The composition of Claim 110 wherein R⁵² is OR⁶⁴ wherein R⁶⁴ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, benzyl and phenyl; wherein each of R⁵³, R⁵⁴ and R⁵⁷ through R⁶³ is independently selected from hydrido, alkyl, cycloalkyl, hydroxy, alkoxy, benzyl and phenyl; wherein each of R⁵⁵ and R⁵⁶ is independently selected from hydrido, alkyl, cycloalkyl, benzyl and phenyl; wherein each of m and n is a number independently selected from zero through three, inclusive.

15 112. The composition of Claim 111 wherein R⁵² is OR⁶⁴ wherein R⁶⁴ is selected from hydrido and lower alkyl; wherein each of R⁵³ through R⁵⁸ is hydrido; wherein each of R⁵⁹ through R⁶³ is independently selected from hydrido, alkyl, hydroxy and alkoxy, with the proviso that two of the R⁵⁹ through R⁶³ substituents are hydroxy; wherein each of m and n is a number independently selected from zero through two, inclusive.

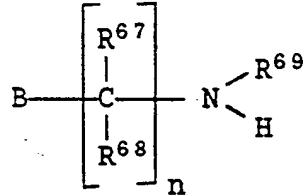
25 113. The composition of Claim 112 wherein said inhibitor compound is 3-(3,4-dihydroxyphenyl)-2-propenoic acid.

30 114. The composition of Claim 103 wherein said dopa-decarboxylase inhibitor is a compound selected from amino-haloalkyl-hydroxyphenyl propionic acids; alpha-halomethyl-phenylalanine derivatives; and indole-substituted halomethylamino acids.

115. The composition of Claim 103 wherein said dopa-decarboxylase inhibitor is a compound selected from isoflavone extracts from fungi and streptomyces; sulfinyl substituted dopa and tyrosine derivatives; hydroxycoumarin derivatives; 1-benzylcyclobutenyl alkyl carbamate derivatives; aryl/thienyl-hydroxylamine derivatives; and β -2-substituted-cyclohepta-pyrrol-8-1H-on-7-yl alanine derivatives.

10 116. The composition of Claim 80 wherein said dopamine- β -hydroxylase inhibitor compound is of the formula

15



20

wherein B is selected from an ethylenic moiety, an acetylenic moiety and an ethylenic or acetylenic moiety substituted with one or more radicals selected from substituted or unsubstituted alkyl, aryl and heteroaryl; wherein each of R⁶⁷ and R⁶⁸ is independently selected from hydrido and alkyl; wherein R⁶⁹ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and

25

wherein n is a number selected from one through five.

30

117. The composition of Claim 116 wherein B is an ethylenic or an acetylenic moiety substituted with an aryl or heteroaryl radical; and wherein n is a number from one through three.

118. The composition of Claim 116 wherein B is an ethylenic or acetylenic moiety incorporating carbon atoms in the beta- and gamma-positions relative to the nitrogen atom; and wherein n is one.

5

119. The composition of Claim 118 wherein said ethylenic or acetylenic moiety is substituted at the gamma carbon with an aryl or heteroaryl radical.

10

120. The composition of Claim 119 wherein said aryl radical is selected from phenyl, 2-thiophene, 3-thiophene, 2-furanyl, 3-furanyl, oxazolyl, thiazolyl and isoxazolyl, any one of which radicals may be substituted with one or more groups selected from halo, hydroxyl, alkyl, haloalkyl, cyano, alkoxy, alkoxyalkyl and cycloalkyl.

15

121. The composition of Claim 120 wherein said aryl radical is selected from phenyl, hydroxyphenyl, 2-thiophene and 2-furanyl; and wherein each of R⁶⁷, R⁶⁸ and R⁶⁹ is hydrido.

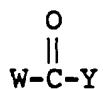
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122. The composition of Claim 121 wherein said inhibitor compound is selected from the group consisting of 3-amino-2-(2'-thienyl)propene; 3-amino-2-(2'-thienyl)butene; 3-(N-methylamino)-2-(2'-thienyl)propene; 3-amino-2-(3'-thienyl)propene; 3-amino-2-(2'-furanyl)propene; 3-amino-2-(3'-furanyl)propene; 1-phenyl-3-aminopropyne; and 3-amino-2-phenylpropene.

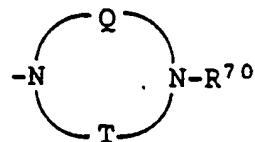
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123. The composition of Claim 121 wherein said inhibitor compound is selected from the group consisting of (\pm)4-amino-3-phenyl-1-butyne; (\pm)4-amino-3-(3'-hydroxyphenyl)-1-butyne; 5 (\pm)4-amino-3-(4'-hydroxyphenyl)-1-butyne; (\pm)4-amino-3-phenyl-1-butene; (\pm)4-amino-3-(3'-hydroxyphenyl)-1-butene; and (\pm)4-amino-3-(4'-hydroxyphenyl)-1-butene.

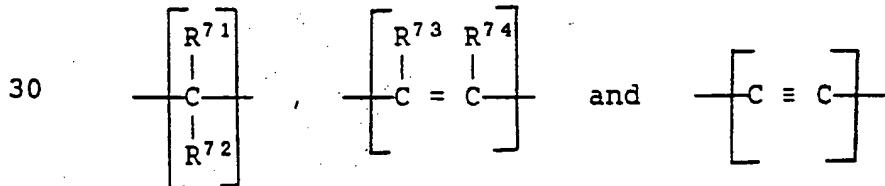
124. The composition of Claim 80 wherein 10 said inhibitor compound is of the formula



wherein W is selected from alkyl, cycloalkyl, 15 alkenyl, alkynyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl; wherein Y is selected from

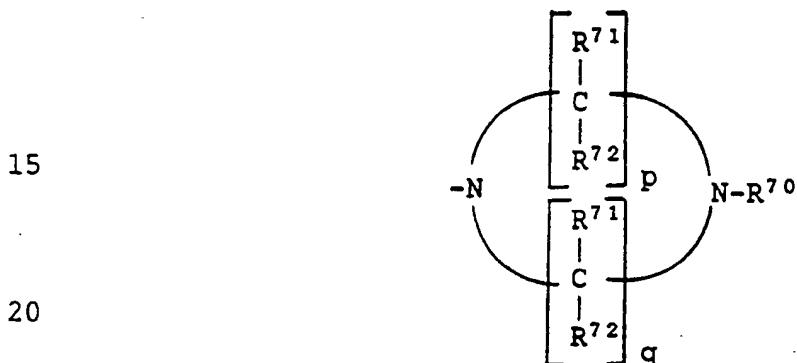


20 wherein R⁷⁰ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxy carbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, 25 alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of Q and T is one or more groups independently selected from



wherein each of R⁷¹ through R⁷⁴ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; or a pharmaceutically-acceptable salt thereof.

125. The composition of Claim 124 wherein W
10 is heteroaryl and Y is



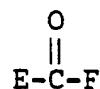
wherein R⁷⁰ is selected from hydrido, alkyl, amino, monoalkylamino, dialkylamino, phenyl and phenalkyl; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive.

126. The composition of Claim 125 wherein R⁷⁰ is selected from hydrido, alkyl, amino and monoalkylamino; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive.

127. The composition of Claim 126 wherein R⁷⁰ is selected from hydrido, alkyl and amino; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three.

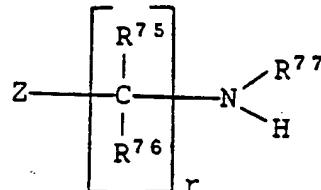
128. The composition of Claim 127 wherein R⁷⁰ is hydrido; wherein each of R⁷¹ and R⁷² is hydrido; and wherein each of p and q is two.

10 129. The composition of Claim 80 wherein said inhibitor compound is of the formula



15 wherein E is selected from alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl; wherein F is selected from

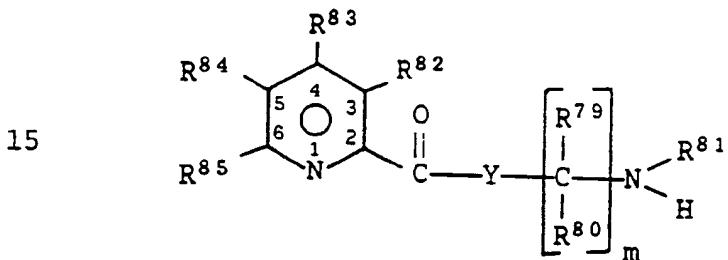
20



25 wherein Z is selected from O, S and N-R⁷⁸; wherein each of R⁷⁵ and R⁷⁶ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, minoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R⁷⁵ and R⁷⁶ may form oxo or thio; wherein r is a number selected from zero through six, inclusive; wherein each of R⁷⁷ and R⁷⁸

is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; or a pharmaceutically-acceptable salt thereof.

10 130. The composition of Claim 80 wherein said dopamine- β -hydroxylase inhibitor compound is of the formula

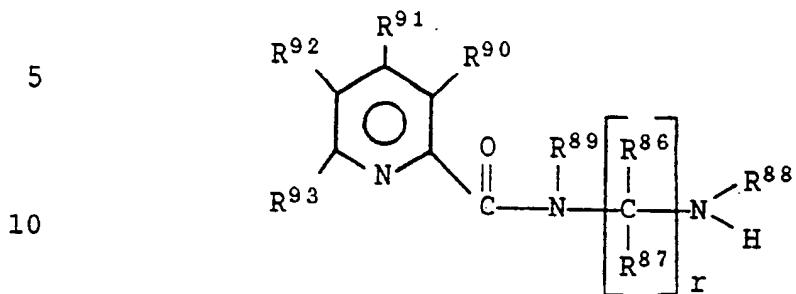


20 wherein each of R⁸² through R⁸⁵ is independently selected from hydrido, alkyl, haloalkyl, mercapto, alkylthio, cyano, alkoxy, alkoxyalkyl and cycloalkyl; wherein Y is selected from oxygen atom and sulfur atom; wherein each of R⁷⁹ and R⁸⁰ is independently selected from hydrido and alkyl; wherein R⁵⁹ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein m is a number from one through six; or a pharmaceutically-acceptable salt thereof.

131. The composition of Claim 130 wherein each of R⁸² through R⁸⁵ is independently selected from hydrido, alkyl and haloalkyl; wherein Y is selected from oxygen atom or nitrogen atom; wherein each of 5 R⁷⁹, R⁸⁰ and R⁸¹ is independently hydrido and alkyl; and wherein m is a number selected from one through four, inclusive.

132. The composition of Claim 131 wherein said inhibitor compound is selected from
10 aminomethyl-5-n-butylthiopicolinate;
aminomethyl-5-n-butylpicolinate;
2'-aminoethyl-5-n-butylthiopicolinate;
2'-aminoethyl-5-n-butylpicolinate;
(2'-amino-1',1'-dimethyl)ethyl-5-n-butylthiopicolinate;
15 (2'-amino-1',1'-dimethyl)ethyl-5-n-butylpicolinate;
(2'-amino-1'-methyl)ethyl-5-n-butylthiopicolinate;
(2'-amino-1'-methyl)ethyl-5-n-butylpicolinate;
3'-aminopropyl-5-n-butylthiopicolinate;
3'-aminopropyl-5-n-butylpicolinate;
20 (2'-amino-2'-methyl)propyl-5-n-butylthiopicolinate;
(2'-amino-2'-methyl)propyl-5-n-butylpicolinate;
(3'-amino-1',1'-dimethyl)propyl-5-n-butylthiopicolinate;
(3'-amino-1',1'-dimethyl)propyl-5-n-butylpicolinate;
(3'-amino-2',2'-dimethyl)propyl-5-n-butylthiopicolinate;
25 (3'-amino-2',2'-dimethyl)propyl-5-n-butylpicolinate;
2'-aminopropyl-5-n-butylthiopicolinate;
2'-aminopropyl-5-n-butylpicolinate;
4'-aminobutyl-5-n-butylthiopicolinate;
4'-amino-3'-methylbutyl-5-n-butylthiopicolinate;
30 (3'-amino-3'-methylbutyl-5-n-butylthiopicolinate; and
(3'-amino-3'-methylbutyl-5-n-butylpicolinate.

133. The composition of Claim 124 wherein
said inhibitor compound is of the formula



wherein each of R⁸⁶, R⁸⁷ and R⁹⁰ through R⁹³ is
independently selected from hydrido, hydroxy, alkyl,
cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy,
15 aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl,
halo, cyano, amino, monoalkylamino, dialkylamino,
carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl
and alkynyl; wherein R⁸⁶ and R⁸⁷ together may form oxo
or thio; wherein r is a number selected from zero
20 through six, inclusive; wherein each of R⁸⁸ and R⁸⁹ is
independently selected from hydrido, alkyl, cycloalkyl,
hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl,
aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl,
amino, cyanoamino, monoalkylamino, dialkylamino,
25 alkylsulfinyl, alkylsulfonyl, arylsulfinyl and
arylsulfonyl.

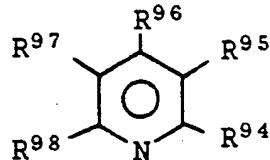
134. The composition of Claim 133 wherein
each of R⁸⁶, R⁸⁷ and R⁹⁰ through R⁹³ is independently
selected from hydrido, hydroxy, alkyl, phenalkyl,
30 phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl,
hydroxyalkyl, halo, amino, monoalkylamino,
dialkylamino, carboxy, carboxyalkyl and alkanoyl;
wherein r is a number selected from zero through four,
inclusive; wherein each of R⁸⁸ and R⁸⁹ is independently
35 selected from hydrido, alkyl, amino, monoalkylamino,
dialkylamino, phenyl and phenalkyl.

135. The composition of Claim 134 wherein each of R⁸⁶, R⁸⁷ and R⁹⁰ through R⁹³ is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; 5 and wherein r is a number selected from zero through three, inclusive; and wherein each of R⁸⁸ and R⁸⁹ is selected from hydrido, alkyl, amino and monoalkylamino.

10 136. The composition of Claim 135 wherein each of R⁹⁰ through R⁹³ is independently selected from hydrido and alkyl; wherein each of R⁸⁶ and R⁸⁷ is hydrido; wherein r is selected from zero, one and two; wherein R⁸⁸ is selected from hydrido, alkyl and amino; and wherein R⁸⁹ is selected from hydrido and 15 alkyl.

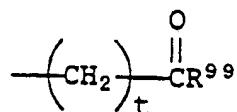
137. The composition of Claim 136 wherein said inhibitor compound is 5-n-butylicolic acid hydrazide.

20 138. The composition of Claim 80 wherein said dopamine-β-hydroxylase inhibitor compound is of the formula



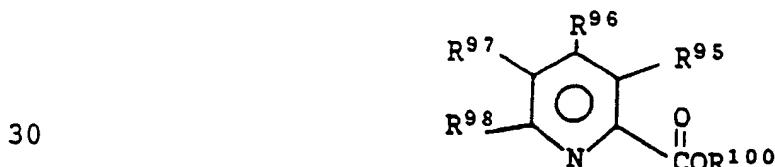
wherein each of R⁹⁴ through R⁹⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, aryloxy, alkoxy, 30 alkylthio, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, amido, alkylamido, hydroxyamino,

carboxyl, carboxyalkyl, alkanoyl, alkenyl,
cycloalkenyl, alkynyl, cyanoamino, carboxyl,
thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro,
alkylsulfonyloxy, formoyl and alkoxycarbonyl; with
5 the proviso that at least one of R⁹⁴ through R⁹⁸ is



10 wherein R⁹⁹ is selected from hydrido, alkyl, hydroxy,
alkoxy, alkylthio, phenyl, phenoxy, benzyl, benzyloxy,
-OR¹⁰⁰ and -N^{R¹⁰¹}_{R¹⁰²}, wherein R¹⁰⁰ is selected from
15 hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenyl
and benzyl and each of R¹⁰¹ and R¹⁰² is independently
selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl,
haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl,
aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino,
20 cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl,
alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein
t is a number selected from zero through four,
inclusive; or a pharmaceutically-acceptable salt
thereof.

25 139. The composition of Claim 138 wherein
said inhibitor compound is of the formula

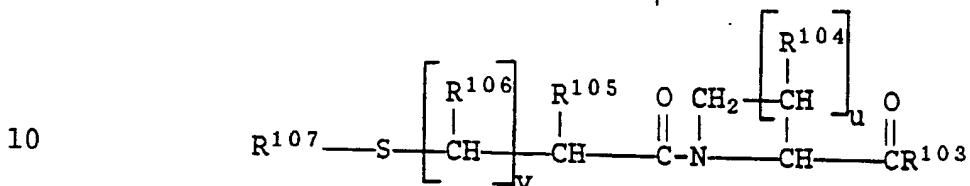


wherein each of R⁹⁵ through R⁹⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, phenyl, benzyl, alkoxy, phenoxy, benzyloxy, alkoxyalkyl, hydroxyalkyl, halo, cyano, amino, 5 monoalkylamino, dialkylamino, amido, alkylamido, hydroxyamino, carboxyl, carboxyalkyl, alkanoyl, cyanoamino, carboxyl, thiocarbamoyl, aminomethyl, nitro, formoyl, formyl and alkoxycarbonyl; and wherein R¹⁰⁰ is selected from hydrido, alkyl, phenyl 10 and benzyl.

140. The composition of Claim 139 wherein said inhibitor compound is selected from
5-n-butylicolic acid;
5-ethylicolic acid;
15 5-picolic acid;
5-nitropicolic acid;
5-aminopicolic acid;
5-N-acetylaminopicolic acid;
5-N-propionylaminopicolic acid;
20 5-N-hydroxyaminopicolic acid;
5-iodopicolic acid;
5-bromopicolic acid;
5-chloropicolic acid;
5-hydroxypicolic acid
25 5-methoxypicolic acid;
5-N-propoxypicolic acid;
5-N-butoxypicolic acid;
5-cyanopicolic acid;
5-carboxylicolic acid;
30 5-n-butyl-4-nitropicolic acid;
5-n-butyl-4-methoxypicolic acid;
5-n-butyl-4-ethoxypicolic acid;
5-n-butyl-4-aminopicolic acid;
5-n-butyl-4-hydroxyaminopicolic acid; and
35 5-n-butyl-4-methylpicolic acid.

141. The composition of Claim 140 wherein said inhibitor compound is 5-n-butylpicolinic acid.

142. The composition of Claim 80 wherein said dopamine- β -hydroxylase inhibitor compound is of
5 the formula



wherein R^{103} is hydrido, hydroxy, alkyl, amino and alkoxy; wherein R^{104} is selected from hydrido, hydroxy and alkyl; wherein each of R^{105} and R^{106} is independently selected from hydrido, alkyl and phenalkyl; wherein R^{107} is selected from hydrido and

15

$$\begin{array}{c} \text{O} \\ || \\ \text{R}^{108}\text{C}- \end{array}$$
 with R^{108} selected from alkyl, phenyl and phenalkyl; wherein u is a number from one to three, inclusive; and wherein v is a number from zero to two, inclusive; or a pharmaceutically-acceptable salt thereof.

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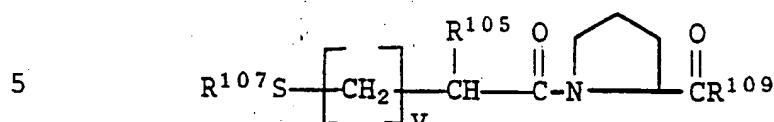
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143. The composition of Claim 142 wherein R^{103} is selected from hydroxy and lower alkoxy; wherein R^{104} is hydrido; wherein R^{105} is selected from hydrido and lower alkyl; wherein R^{106} is hydrido; wherein R^{107} is selected from hydrido and

30

$$\begin{array}{c} \text{O} \\ || \\ \text{R}^{108}\text{C}- \end{array}$$
 with R^{108} selected from lower alkyl and phenyl; wherein u is two; and wherein v is a number from zero to two, inclusive.

144. The composition of Claim 143 wherein said inhibitor compound is of the formula



wherein R^{109} is selected from hydroxy and lower alkyl; wherein R^{105} is selected from hydrido and lower alkyl; wherein R^{107} is selected from hydrido and

10 O
 ||
 $\text{R}^{108}\text{C}-$ with R^{108} selected from lower alkyl and phenyl and v is a number from zero to two, inclusive.

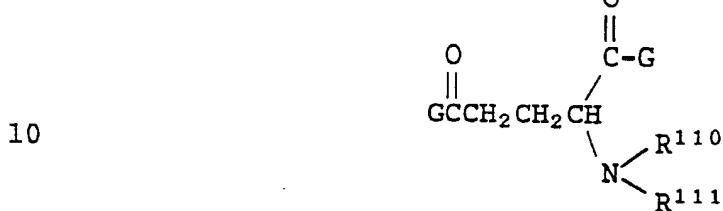
15 R^{109} is hydroxy; wherein R^{105} is hydrido or methyl; wherein R^{107} is hydrido or acetyl; and wherein n is a number from zero to two, inclusive.

20 146. The composition of Claim 145 wherein said inhibitor compound is 1-(3-mercaptop-2-methyl-1-oxopropyl)-L-proline.

147. The composition of Claim 79 wherein said precursor compound providing the second residue has a reactable acid moiety.

148. The composition of Claim 147 wherein said second residue precursor compound of said conjugate is selected from a class of glutamic acid derivatives of the formula

5



10

wherein each of R^{110} and R^{111} may be independently selected from hydrido, alkylcarbonyl, alkoxy carbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-OR^{112}$, $-SR^{113}$ and $>NR^{114}$ with each of R^{112} , R^{113} and R^{114} independently selected from hydrido and alkyl; with the proviso that said glutamic acid is selected such that formation of the cleavable amide bond occurs at the gamma-position carbon of said gamma-glutamic acid residue.

15

20

25

149. The composition of Claim 148 wherein said second residue precursor compound of said conjugate is the glutamic acid derivative gamma-glutamic acid.

150. The composition of Claim 149 wherein R^{110} is hydrido, and R^{111} is selected from

30

$-CR^{115}$ wherein R^{115} is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

151. The composition of Claim 150 wherein said second residue precursor compound of said conjugate is the glutamic acid derivative is N-acetyl- γ -glutamic acid.

5 152. The composition of Claim 80 wherein said conjugate comprises a first residue provided by a dopamine- β -hydroxylase inhibitor compound and a second residue provided by a gamma glutamic acid derivative.

10 153. The composition of Claim 152 wherein said dopamine- β -hydroxylase inhibitor is fusaric acid or fusaric acid hydrazide and said gamma glutamic acid derivative is N-acetyl- γ -glutamic acid.

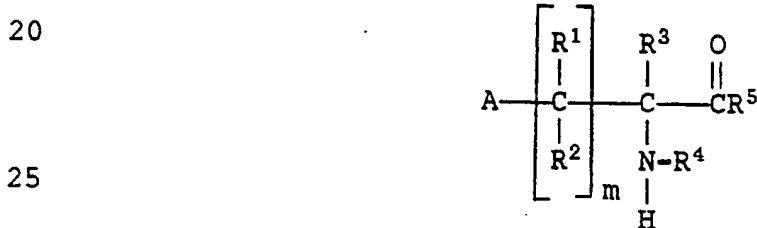
15 154. The composition of Claim 153 wherein said conjugate is N-acetyl- γ -glutamyl fusaric acid hydrazide.

20 155. A method for treating a hypertensive-related disorder or a sodium-retaining disorder, said method comprising administering to a patient afflicted with or susceptible to said disorder a therapeutically-effective amount of a conjugate comprising a first residue and a second residue, said first and second residues connected together by a cleavable bond, wherein said first residue is derived from an
25 inhibitor compound capable of inhibiting biosynthesis of an adrenergic neurotransmitter, and wherein said second residue is capable of being cleaved from the first residue by an enzyme located predominantly in the kidney.

156. The method of Claim 155 wherein said first and second residues are provided by precursor compounds wherein the precursor compound of one of said first and second residues has a reactable carboxylic acid moiety and the precursor of the other of said first and second residues has a reactable amino moiety or a moiety convertible to a reactable amino moiety, whereby a cleavable bond may be formed between said carboxylic acid moiety and said amino moiety.

157. The method of Claim 156 wherein said inhibitor compound providing said first residue is selected from tyrosine hydroxylase inhibitor compounds, dopa-decarboxylase inhibitor compounds, dopamine- β -hydroxylase inhibitor compounds, and mimics of said inhibitor compounds.

158. The method of Claim 157 wherein said tyrosine hydroxylase inhibitor compound is of the formula

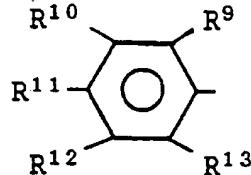


wherein each of R¹ through R³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R⁴ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl,

carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein R⁵ is selected from -OR⁶ and

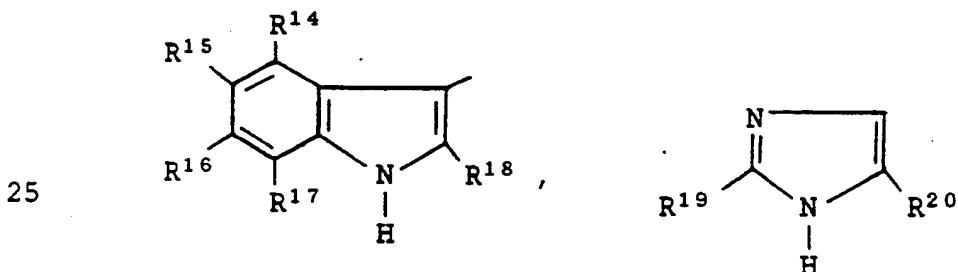
5 $\begin{array}{c} \text{R}^7 \\ | \\ -\text{N}- \\ | \\ \text{R}^8 \end{array}$, wherein R⁶ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl, and
 10 wherein each of R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxy carbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkyl-
 15 sulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; aralkyl; wherein m is a number selected from zero through six;

wherein A is a phenyl ring of the formula



wherein each of R⁹ through R¹³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy, formyl and a substituted or unsubstituted 5- or 6-membered heterocyclic ring selected from the group consisting of pyrrol-1-yl, 2-carboxy-pyrrol-1-yl, imidazol-2-ylamino, indol-1-yl, carbozol-

9-yl, 4,5-dihydro-4-hydroxy-4-trifluoromethylthiazol-3-yl, 4-trifluoromethylthiazol-2-yl, imidazol-2-yl and 4,5-dihydroimidazol-2-yl; wherein any two of the R⁹ through R¹³ groups may be taken together to form a benzoheterocyclic ring selected from the group consisting of indolin-5-yl, 1-(N-benzoylcarbamimidoyl)indolin-5-yl, 1-carbamimidoylindolin-5-yl, 1H-2-oxindol-5-yl, insol-5-yl, 2-mercaptopbenzimidazol-5(6)-yl, 2-aminobenzimidazol-5-(6)-yl, 2-methanesulfonamido-benzimidazol-5(6)-yl, 1H-benzoxanol-2-on-6-yl, 2-aminobenzothiazol-6-yl, 2-amino-4-mercaptopbenzothiazol-6-yl, 2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-1,3-dimethyl-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 4-methyl-2(H)-oxoquinolin-6-yl, quinoxalin-6-yl, 2-hydroxyquinoxalin-6-yl, 2-hydroxquinoxalin-7-yl, 2,3-dihydroxyquinoxalin-6-yl and 2,3-dihydro-3(4H)-oxo-1,4-benzoxazin-7-yl; 5-hydroxy-4H-pyran-4-on-2-yl, 2-hydroxypyrid-4-yl, 2-aminopyrid-4-yl, 2-carboxypyrid-4-yl or tetrazolo[1,5-a]pyrid-7-yl; and wherein A may be selected from

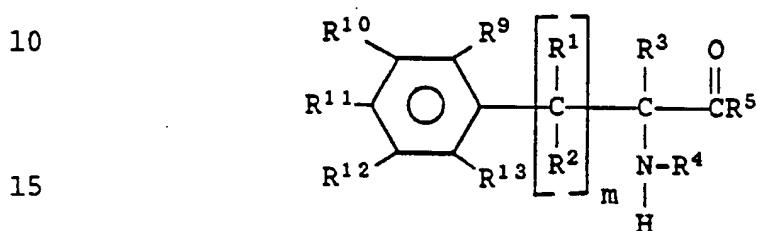


and -N(R²¹)₂

wherein each of R¹⁴ through R²⁰ is independently selected from hydrido, alkyl, hydroxy, hydroxyalkyl, alkoxy, cycloalkyl, cycloalkylalkyl, halo, haloalkyl, aryloxy, alkoxycarboxyl, aryl, aralkyl, cyano, cyanoalkyl, amino, monoalkylamino and dialkylamino,

wherein each of R²¹ and R²² is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; or a pharmaceutically-acceptable salt thereof.

159. The method of Claim 158 wherein said inhibitor compound is of the formula



wherein each of R¹ and R² is hydrido; wherein m is one;
wherein R³ is selected from alkyl, alkenyl and alkynyl;
wherein R⁴ is selected from hydrido, alkyl,
20 cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl,
alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxy carbonyl,
carboxyl, amino, cyanoamino, monoalkylamino,
dialkylamino, alkylsulfinyl, alkylsulfonyl,
arylsulfinyl and arylsulfonyl; wherein R⁵ is selected
25 from OR⁶ and

$\begin{array}{c} \text{R}^7 \\ | \\ -\text{N}- \\ | \\ \text{R}^8 \end{array}$, wherein R^6 is selected from

30 hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl and phenyl, and wherein each of R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino,

alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R⁹ through R¹³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxycarbonyl, 5 alkoxycarbonyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, pyrrol-1-yl 10 2-carboxypyrrrol-1-yl, imidazol-2-ylamino, indol-1-yl, carbazol-9-yl, 4,5-dihydro-4-trifluoromethylthiazol-3-yl, 4-trifluoromethylthiazol-2-yl, imidazol-2-yl and 4,5-dihydroimidazol-2-yl, and wherein any two of the R⁹ through R¹³ groups may be taken together to form a benzoheterocyclic ring selected from the group 15 consisting of indolin-5-yl, 1-(N-benzoylcarbamimidoyl)-indolin-5-yl, 1-carbamimidoylindolin-5-yl, 1H-2-oxindol-5-yl, indol-5-yl, 2-mercaptopbenzimidazol-5(6)-yl, 2-aminobenzimidazol-5(6)-yl, 2-methanesulfonamido-benzimidazol-5(6)-yl, 1H-benzoxanol-2-on-6-yl, 2-amino-benzothiazol-6-yl, 2-amino-4-mercaptopbenzothiazol-6-yl, 20 2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 1,3-dihydro-1,3-dimethyl-2,2-dioxo-2,1,3-benzothiadiazol-5-yl, 4-methyl-2(H)-oxoquinolin-6-yl, quinoxalin-6-yl, 2-hydroxyquinoxalin-6-yl, 2-hydroxquinoxalin-7-yl, 2,3-dihydroxyquinoxalin-6-yl and 2,3-dihydro-3(4H)-oxo-1,4-benzoxazin-7-yl; 25 wherein R⁵ is -CH=CH₂ or -C≡CH; wherein R⁶ is selected from hydrido, alkyl, hydroxy, hydroxyalkyl, alkoxy, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino; and wherein each of R⁷ and R⁸ independently is 30 selected from hydrido, alkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; or a pharmaceutically-acceptable salt thereof.

160. The method of Claim 159 wherein said inhibitor compound is selected from the group consisting of
- 4-cyanoamino- α -methylphenylalanine;
- 5 3-carboxy- α -methylphenylalanine;
- 3-cyano- α -methylphenylalanine methyl ester;
- α -methyl-4-thiocarbamoylphenylalanine methyl ester;
- 4-(aminomethyl)- α -methylphenylalanine;
- 4-guanidino- α -methylphenylalanine;
- 10 3-hydroxy-4-methanesulfonamido- α -methylphenylalanine;
- 3-hydroxy-4-nitro- α -methylphenylalanine;
- 4-amino-3-methanesulfonyloxy- α -methylphenylalanine;
- 3-carboxymethoxy-4-nitro- α -methylphenylalanine;
- α -methyl-4-amino-3-nitrophenylalanine;
- 15 3,4-diamino- α -methylphenylalanine;
- α -methyl-4-(pyrrol-1-yl)phenylalanine;
- 4-(2-aminoimidazol-1-yl)- α -methylphenylalanine;
- 4-(imidazol-2-ylamino)- α -methylphenylalanine;
- 4-(4,5-dihydro-4-hydroxy-4-trifluoromethyl-thiazol-2-yl)-
- 20 α -methylphenylalanine methyl ester;
- α -methyl-4-(4-trifluoromethylthiazol-2-yl)phenylalanine;
- α -methyl-3-(4-trifluoromethylthiazol-2-yl)-phenyl-
- alanine;
- 4-(imidazol-2-yl)- α -methylphenylalanine;
- 25 4-(4,5-dihydroimidazol-2-yl)- α -methylphenylalanine;
- 3-(imidazol-2-yl)- α -methylphenylalanine;
- 3-(4,5-dihydroimidazol-2-yl)- α -methylphenylalanine;
- 4-(imidazol-2-yl)phenylalanine;
- 4,5-dihydroimidazol-2-yl)phenylalanine;
- 30 3-(imidazol-2-yl)phenylalanine;
- 3-(2,3-dihydro-1H-indol-4-yl)- α -methylalanine;
- α -methyl-3-(1H-2-oxindol-5-yl)alanine;
- 3-[1-(N-benzoylcarbamimidoyl)-2,3-dihydro-1H-
- indol-5-yl)]- α -methylalanine;
- 35 3-(1-carbamimidoyl-2,3-dihydro-1H-indol-5-yl- α -

methylalanine;
3-(1H-indol-5-yl)- α -methylalanine;
3-(benzimidazol-2-thione-5-yl)- α -methylalanine;
3-(2-aminobenzimidazol-5-yl-2-methylalanine;
5 2-methyl-3-(benzoxazol-2-on-6-yl)alanine;
3-(2-aminobenzothiazol-6-yl)-2-methylalanine;
3-(2-amino-4-mercaptobenzothiazol-6-yl)-2-
methylalanine;
3-(2-aminobenzothiazol-6-yl)alanine;
10 2-methyl-3-(2,1,3-benzothiadiazol-5-yl)alanine;
3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)-2-
methylalanine-2,2-dioxide;
3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)-2-methyl-
alanine-2,2-dioxide methyl ester;
15 3-(1,3-dihydrobenzo-2,1,3-thiadiazol-5-yl)alanine
2,2-dioxide;
3-(1,3-dihydro-1,3-dimethylbenzo-2,1,3-thiadiazol-5-
yl)-2-methylalanine 2,2-dioxide;
 α -methyl-3-[4-methyl-2(1H)-oxoquinolin-6-yl]alanine;
20 3-[4-methyl-2(1H)-oxoquinolin-6-yl]alanine;
2-methyl-3-(quinoxalin-6-yl)alanine;
2-methyl-3-(2-hydroxyquinoxalin-6-yl)alanine;
2-methyl-3-(2-hydroxyquinoxalin-7-yl)alanine;
3-(2,3-dihydroxyquinoxalin-6-yl)-2-methylalanine;
25 3-(quinoxalin-6-yl)alanine;
3-(2,3-dihydroxyquinoxalin-6-yl)alanine;
3-(1,4-benzoxazin-3-one-6-yl)-2-methylalanine;
3-(1,4-benzoxazin-3-one-7-yl)alanine;
3-(5-hydroxy-4H-pyran-4-on-2-yl)-2-methylalanine;
30 3-(2-hydroxy-4-pyridyl)-2-methylalanine;
3-(2-carboxy-4-pyridyl)-2-methylamine;
 α -methyl-4-(pyrrol-1-yl)phenylalanine;
 α -ethyl-4-(pyrrol-1-yl)phenylalanine;
 α -propyl-4-(pyrrol-1-yl)phenylalanine;
35 4-[2-(carboxy)pyrrol-1-yl]phenylalanine;

α -methyl-4-(pyrrol-1-yl)phenylalanine;
3-hydroxy- α -methyl-4-(pyrrol-1-yl)phenylalanine;
3-methoxy- α -methyl-4-(pyrrol-1-yl)phenylalanine;
4-methoxy- α -methyl-3-(pyrrol-1-yl)phenylalanine;
5 4-(indol-1-yl)- α -methylphenylalanine;
4-(carbazol-9-yl)- α -methylphenylalanine;
2-methyl-3-(2-methanesulfonylamidobenzimidazol-
5-yl)alanine;
2-methyl-3-(2-amino-4-pyridyl)alanine;
10 2-methyl-3[tetrazolo-(1,5)- α -pyrid-7-yl]alanine;
D,L- α -methyl- β -(4-hydroxy-3-methyl)phenylalanine;
D,L- α -methyl- β -(4-hydroxy-3-phenyl)phenylalanine;
D,L- α -methyl- β -(4-hydroxy-3-benzyl)phenylalanine;
D,L- α -methyl- β -(4-methoxy-3-cyclohexyl)phenyl-
15 alanine;
 α , β , β -trimethyl- β -(3,4-dihydroxyphenyl)alanine;
 α , β , β -trimethyl- β -(4-hydroxyphenyl)alanine;
N-methyl- α , β , β -trimethyl- β -(3,4-dihydroxyphenyl)-
alanine;
20 D,L- α , β , β -trimethyl- β -(3,4-dihydroxyphenyl)alanine;
 α , β , β -trimethyl- β -(3,4-dimethoxyphenyl)alanine;
L- α -methyl- β -3,4-dihydroxyphenylalanine;
L- α -ethyl- β -3,4-dihydroxyphenylalanine;
L- α -propyl- β -3,4-dihydroxyphenylalanine;
25 L- α -butyl- β -3,4-dihydroxyphenylalanine;
L- α -methyl- β -2,3-dihydroxyphenylalanine;
L- α -ethyl- β -2,3-dihydroxyphenylalanine;
L- α -propyl- β -2,3-dihydroxyphenylalanine;
L- α -butyl- β -2,3-dihydroxyphenylalanine;
30 L- α -methyl-4-chloro-2,3-dihydroxyphenylalanine;
L- α -ethyl-4-chloro-2,3-dihydroxyphenylalanine;
L- α -propyl-4-chloro-2,3-dihydroxyphenylalanine;
L- α -butyl-4-chloro-2,3-dihydroxyphenylalanine;
L- α -ethyl- β -4-methyl-2,3-dihydroxyphenylalanine;
35 L- α -methyl- β -4-methyl-2,3-dihydroxyphenylalanine;

L- α -propyl- β -4-methyl-2,3-dihydroxyphenylalanine;
L- α -butyl- β -4-methyl-2,3-dihydroxyphenylalanine;
L- α -methyl- β -4-fluoro-2,3-dihydroxyphenylalanine;
L- α -ethyl- β -4-fluoro-2,3-dihydroxyphenylalanine;
5 L- α -propyl- β -4-fluoro-2,3-dihydroxyphenylalanine;
L- α -butyl- β -4-fluoro-2,3-dihydroxyphenylalanine;
L- α -methyl- β -4-trifluoromethyl-2,3-dihydroxyphenyl-
alanine
10 L- α -ethyl- β -4-trifluoromethyl-2,3-dihydroxyphenyl-
alanine
L- α -propyl- β -4-trifluoromethyl-2,3-dihydroxyphenyl-
alanine
L- α -butyl- β -4-trifluoromethyl-2,3-dihydroxyphenyl-
alanine
15 L- α -methyl- β -3,5-dihydroxyphenylalanine;
L- α -ethyl- β -3,5-dihydroxyphenylalanine;
L- α -propyl- β -3,5-dihydroxyphenylalanine;
L- α -butyl- β -3,5-dihydroxyphenylalanine;
L- α -methyl- β -4-chloro-3,5-dihydroxyphenylalanine;
20 L- α -ethyl- β -4-chloro-3,5-dihydroxyphenylalanine;
L- α -propyl- β -4-chloro-3,5-dihydroxyphenylalanine;
L- α -butyl- β -4-chloro-3,5-dihydroxyphenylalanine;
L- α -methyl- β -4-fluoro-3,5-dihydroxyphenylalanine;
L- α -ethyl- β -4-fluoro-3,5-dihydroxyphenylalanine;
25 L- α -propyl- β -4-fluoro-3,5-dihydroxyphenylalanine;
L- α -butyl- β -4-fluoro-3,5-dihydroxyphenylalanine;
L- α -methyl- β -4-trifluoromethyl-3,5-dihydroxyphenyl-
alanine;
L- α -ethyl- β -4-trifluoromethyl-3,5-dihydroxyphenyl-
30 alanine;
L- α -propyl- β -4-trifluoromethyl-3,5-dihydroxyphenyl-
alanine;
L- α -butyl- β -4-trifluoromethyl-3,5-dihydroxyphenyl-
alanine;
35 L- α -methyl-2,5-dihydroxyphenylalanine;

L- α -ethyl-2,5-dihydroxyphenylalanine;
L- α -propyl-2,5-dihydroxyphenylalanine;
L- α -butyl-2,5-dihydroxyphenylalanine;
L- α -methyl- β -4-chloro-2,5-dihydroxyphenylalanine;
5 L- α -ethyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -propyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -butyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -methyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -ethyl- β -4-chloro-2,5-dihydroxyphenylalanine;
10 L- α -propyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -butyl- β -4-chloro-2,5-dihydroxyphenylalanine;
L- α -methyl- β -methyl-2,5-dihydroxyphenylalanine;
L- α -ethyl- β -methyl-2,5-dihydroxyphenylalanine;
15 L- α -propyl- β -methyl-2,5-dihydroxyphenylalanine;
L- α -butyl- β -methyl-2,5-dihydroxyphenylalanine;
L- α -methyl- β -4-trifluoromethyl-2,5-dihydroxyphenyl-
alanine;
L- α -ethyl- β -4-trifluoromethyl-2,5-dihydroxyphenyl-
alanine;
20 L- α -propyl- β -4-trifluoromethyl-2,5-dihydroxyphenyl-
alanine;
L- α -butyl- β -4-trifluoromethyl-2,5-dihydroxyphenyl-
alanine;
L- α -methyl- β -3,4,5-trihydroxyphenylalanine;
25 L- α -ethyl- β -3,4,5-trihydroxyphenylalanine;
L- α -propyl- β -3,4,5-trihydroxyphenylalanine;
L- α -butyl- β -3,4,5-trihydroxyphenylalanine;
L- α -methyl- β -2,3,4-trihydroxyphenylalanine;
L- α -ethyl- β -2,3,4-trihydroxyphenylalanine;
30 L- α -propyl- β -2,3,4-trihydroxyphenylalanine;
L- α -butyl- β -2,3,4-trihydroxyphenylalanine;
L- α -methyl- β -2,4,5-trihydroxyphenylalanine;
L- α -ethyl- β -2,4,5-trihydroxyphenylalanine;
L- α -propyl- β -2,4,5-trihydroxyphenylalanine;
35 L- α -butyl- β -2,4,5-trihydroxyphenylalanine;

L-phenylalanine;
D,L- α -methylphenylalanine;
D,L-3-iodophenylalanine;
D,L-3-iodo- α -methylphenylalanine;
5 3-iodotyrosine;
3,5-diiodotyrosine;
L- α -methylphenylalanine;
D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)alanine;
D,L- α -methyl- β -(4-methoxy-3-benzylphenyl)alanine;
10 D,L- α -methyl- β -(4-hydroxy-3-benzylphenyl)alanine;
D,L- α -methyl- β -(4-methoxy-3-cyclohexylphenyl)alanine;
D,L- α -methyl- β -(4-hydroxy-3-cyclohexylphenyl)alanine;
D,L- α -methyl- β -(4-methoxy-3-methylphenyl)alanine;
D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)alanine;
15 N,O-dibenzylloxycarbonyl-D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)alanine;
N,O-dibenzylloxycarbonyl-D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)alanine amide;
D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)-
20 alanine amide;
N,O-diacetyl-D,L- α -methyl- β -(4-hydroxy-3-methylphenyl)alanine;
D,L-N-acetyl- α -methyl- β -(4-hydroxy-3-methylphenyl)-
alanine;
25 L-3,4-dihydroxy- α -methylphenylalanine;
L-4-hydroxy-3-methoxy- α -methylphenylalanine;
L-3,4-methylene-dioxy- α -methylphenylalanine;
2-vinyl-2-amino-3-(2-methoxyphenyl)propionic acid;
2-vinyl-2-amino-3-(2,5-dimethoxyphenyl)propionic acid;
30 2-vinyl-2-amino-3-(2-imidazolyl)propionic acid;
2-vinyl-2-amino-3-(2-methoxyphenyl)propionic acid
ethyl ester;
 α -methyl- β -(2,5-dimethoxyphenyl)alanine;
 α -methyl- β -(2,5-dihydroxyphenyl)alanine;
35 α -ethyl- β -(2,5-dimethoxyphenyl)alanine;

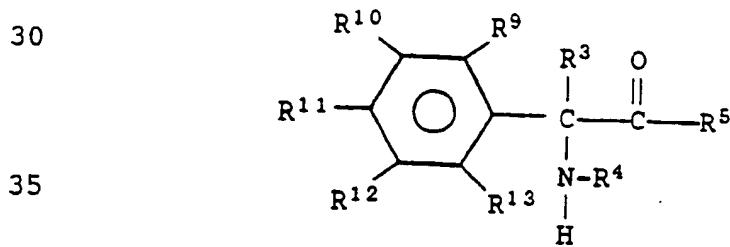
α -ethyl- β -(2,5-dihydroxyphenyl)alanine;
 α -methyl- β -(2,4-dimethoxyphenyl)alanine;
 α -methyl- β -(2,4-dihydroxyphenyl)alanine;
5 α -ethyl- β -(2,4-dimethoxyphenyl)alanine;
 α -methyl- β -(2,5-dimethoxyphenyl)alanine
 ethyl ester;
2-ethynyl-2-amino-3-(3-indolyl)propionic acid;
2-ethynyl-2,3-(2-methoxyphenyl)propionic acid;
10 2-ethynyl-2,3-(5-hydroxyindol-3-yl)propionic acid;
2-ethynyl-2-amino-3-(2,5-dimethoxyphenyl)propionic acid;
2-ethynyl-2-amino-3-(2-imidazolyl)propionic acid;
2-ethynyl-2-amino-3-(2-methoxyphenyl)propionic acid
 ethyl ester;
15 3-carbomethoxy-3-(4-benzyloxybenzyl)-3-aminoprop-1-yne;
 α -ethynyltyrosine hydrochloride;
 α -ethynyltyrosine;
 α -ethynyl-m-tyrosine;
 α -ethynyl- β -(2-methoxyphenyl)alanine;
20 α -ethynyl- β -(2,5-dimethoxyphenyl)alanine; and
 α -ethynylhistidine.

161. The method of Claim 159 wherein at least one of R¹⁰, R¹¹ and R¹² is selected from hydroxy, alkoxy, aryloxy, aralkoxy and alkoxycarbonyl.

25 162. The method of Claim 161 wherein said inhibitor compound is selected from the group consisting of
 α -methyl-3-(pyrrol-1-yl)tyrosine;
 α -methyl-3-(4-trifluoromethylthiazol-2-yl)tyrosine;
30 3-(imidazol-2-yl)- α -methyltyrosine;
L- α -methyl-m-tyrosine;
L- α -ethyl-m-tyrosine;
L- α -propyl-m-tyrosine;

L- α -butyl-m-tyrosine;
L- α -methyl-p-chloro-m-tyrosine;
L- α -ethyl-p-chloro-m-tyrosine;
L- α -butyl-p-chloro-m-tyrosine;
5 L- α -methyl-p-bromo-m-tyrosine;
L- α -ethyl-p-bromo-m-tyrosine;
L- α -butyl-p-bromo-m-tyrosine;
L- α -methyl-p-fluoro-m-tyrosine;
L- α -methyl-p-iodo-m-tyrosine;
10 L- α -ethyl-p-iodo-m-tyrosine;
L- α -methyl-p-methyl-m-tyrosine;
L- α -methyl-p-ethyl-m-tyrosine;
L- α -ethyl-p-ethyl-m-tyrosine;
L- α -ethyl-p-methyl-m-tyrosine;
15 L- α -methyl-p-butyl-m-tyrosine;
L- α -methyl-p-trifluoromethyl-m-tyrosine;
L-3-iodotyrosine;
L-3-chlorotyrosine;
L-3,5-diiodotyrosine;
20 L- α -methyltyrosine;
D,L- α -methyltyrosine;
D,L-3-iodo- α -methyltyrosine;
L-3-bromo- α -methyltyrosine;
D,L-3-bromo- α -methyltyrosine;
25 L-3-chloro- α -methyltyrosine;
D,L-3-chloro- α -methyltyrosine; and
2-vinyl-2-amino-3-(4-hydroxyphenyl)propionic acid.

163. The method of Claim 158 wherein said inhibitor compound is of the formula



wherein R³ is selected from alkyl, alkenyl and alkynyl; wherein R⁴ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl,

5 amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein m is a number selected from zero through five, inclusive; wherein R⁵ is selected from OR⁶ and

10 $\begin{array}{c} \text{R}^7 \\ | \\ -\text{N}- \\ | \\ \text{R}^8 \end{array}$, wherein R⁶ is selected from

hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenalkyl and phenyl, and wherein each of R⁷ and R⁸ is independently selected from hydrido, alkyl, cycloalkyl,

15 hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and aryl-

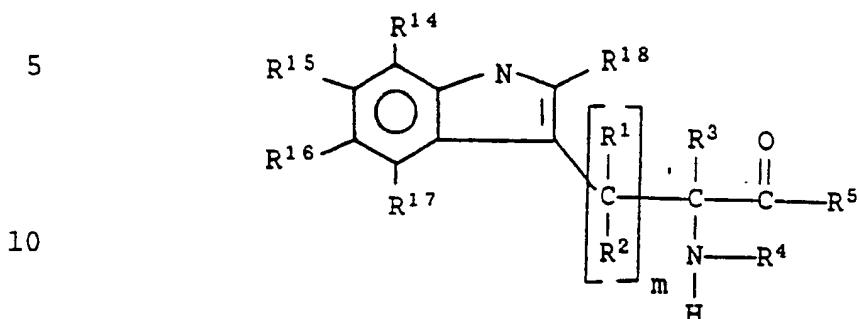
20 sulfonyl; wherein each of R⁹ through R¹³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxycarbonyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, haloalkyl, alkoxycarbonyl, hydroxyalkyl, halo, cyano, amino,

25 monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

164. The method of Claim 163 wherein at least one of R¹⁰, R¹¹ and R¹² is selected from hydroxy, alkoxy, aryloxy, aralkoxy and alkoxycarbonyl.

30 165. The method of Claim 164 wherein said inhibitor compound is selected from the group consisting of methyl(+) -2-(4-hydroxyphenyl)glycinate; isopropyl and 3-methyl butyl esters of (+)-2-(4-hydroxyphenyl)-glycine; (+)-2-(4-hydroxyphenyl)glycine; (-)-2-(4-hydroxyphenyl)glycine; (+)-2-(4-methoxyphenyl)-glycine; and (+)-2-(4-hydroxyphenyl)glycinamide.

166. The method of Claim 158 wherein said inhibitor compound is of the formula



wherein each of R¹ and R² is hydrido; wherein R³ is selected from alkyl, alkenyl and alkynyl; wherein R⁴ is selected from hydrido, alkyl, cycloalkyl, hydroxy-alkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein m is a number selected from zero through five, inclusive; wherein each of R¹⁴ through R¹⁷ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cyclo-alkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy and formyl.

167. The method of Claim 166 wherein said inhibitor compound is selected from the group consisting of
 L- α -methyltryptophan;
 D,L-5-methyltryptophan;
 D,L-5-chlorotryptophan;

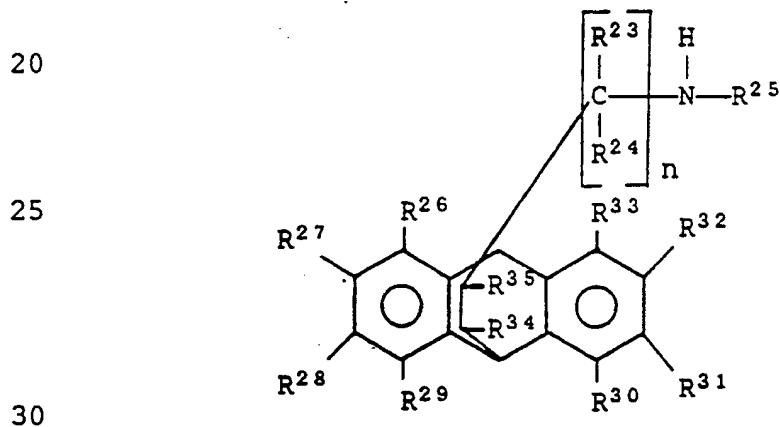
D,L-5-bromotryptophan;
 D,L-5-iodotryptophan;
 L-5-hydroxytryptophan;
 D,L-5-hydroxy- α -methyltryptophan;
 5 α -Ethynyltryptophan;
 5-Methoxymethoxy- α -ethynyltryptophan; and
 5-Hydroxy- α -ethynyltryptophan.

168. The method of Claim 158 wherein A is

10 $\begin{array}{c} R^{21} \\ | \\ -N- \\ | \\ R^{22} \end{array}$, and m is a number selected from zero to
 three, inclusive.

169. The method of Claim 168 wherein said
 inhibitor compound is selected from the group consisting
 15 of 2-vinyl-2-amino-5-aminopentanoic acid and
 2-ethynyl-2-amino-5-aminopentanoic acid.

170. The method of Claim 158 wherein said
 inhibitor compound is of the formula

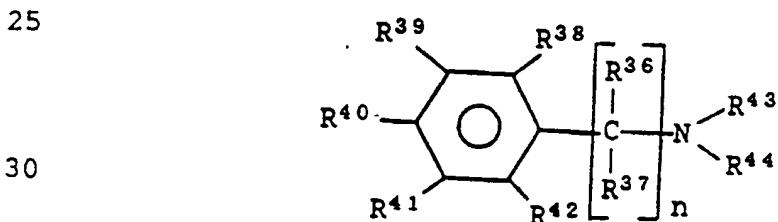


wherein each of R²³ and R²⁴ is independently
 selected from hydrido, hydroxy, alkyl, cycloalkyl,
 cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy,

aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R²⁵ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxy carbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of R²⁶ through R³⁵ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, carboxyl, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, alkoxy and formyl; wherein n is a number selected from zero to five, inclusive; or a pharmaceutically-acceptable salt thereof.

171. The method of Claim 170 wherein said inhibitor compound is benzoctamine.

172. The method of Claim 157 wherein said inhibitor compound is a dopa-decarboxylase inhibitor of the formula



wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, cycloalkyl,

cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy,
alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano,
amino, monoalkylamino, dialkylamino, carboxyl,
carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl,
5 alkynyl, cyanoamino, cyano, thiocarbamoyl,
aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy,
carboxyalkoxy and formyl; wherein n is a whole number
from zero through four; wherein each of R⁴³ and R⁴⁴ is
independently selected from hydrido, alkyl,
10 cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl,
alkoxyalkyl, aralkyl, aryl, alkanoyl, alcoxycarbonyl,
carboxyl, amino, cyanoamino, monoalkylamino,
dialkylamino, alkylsulfinyl, alkylsulfonyl,
arylsulfinyl, arylsulfonyl, alkenyl, cycloalkenyl
15 and alkynyl, with the proviso that R⁴³ and R⁴⁴ cannot
both be carboxyl at the same time, and with the
further proviso that at least one of R⁴³ through R⁴⁴
is a primary or secondary amino group; or a pharmaceutically-acceptable salt thereof.

20 173. The method of Claim 172 wherein each of
R³⁶ through R⁴² is independently selected from
hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl,
aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl,
haloalkyl, hydroxyalkyl, halo, amino, monoalkylamino,
25 dialkylamino, carboxyl, carboxyalkyl, alkanoyl,
alkenyl, cycloalkenyl, alkynyl, cyanoamino,
cyano, aminomethyl, carboxyalkoxy and formyl; wherein
n is a whole number from one through three; wherein
each of R⁴³ and R⁴⁴ is independently selected from
30 hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl,
aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl, amino,
monoalkylamino, dialkylamino, carboxyl, carboxyalkyl
and alkanoyl.

174. The method of Claim 173 wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, benzyl, phenyl, alkoxy, benzyloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, 5 amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, cyanoamino, cyano, aminomethyl, carboxyl, carboxyalkoxy and formyl; wherein n is one or two; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, benzyl, 10 phenyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl and alkanoyl.

175. The method of Claim 174 wherein each of R³⁶ through R⁴² is independently selected from hydrido, hydroxy, alkyl, alkoxy, haloalkyl, 15 hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl, aminomethyl, carboxyalkoxy and formyl; wherein n is one or two; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, 20 haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl and carboxyalkyl.

176. The method of Claim 175 wherein each of R³⁶ and R⁴² is hydrido and n is one; wherein each of R³⁸ through R⁴² is independently selected from hydroxy, 25 alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, 30 carboxyl and carboxyalkyl.

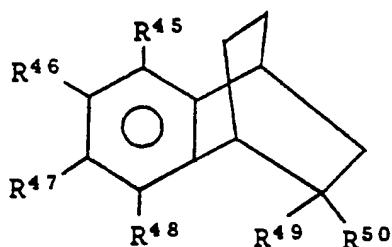
177. The method of Claim 176 wherein said inhibitor compound is selected from (2,3,4-trihydroxy)-benzylhydrazine; 1-(D,L-seryl-2-(2,3,4-trihydroxybenzyl))-hydrazine; and 1-(3-hydroxylbenzyl)-1-methylhydrazine.

5 178. The method of Claim 175 wherein each of R³⁶ and R³⁷ is independently selected from hydrido, alkyl and amino and n is two; wherein each of R³⁸ through R⁴² is independently selected from hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, 10 monoalkylamino, carboxyl, carboxyalkyl, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴³ and R⁴⁴ is independently selected from hydrido, alkyl, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl and carboxyalkyl.

15 179. The method of Claim 178 wherein said inhibitor compound is selected from 2-hydrazino-2-methyl-3-(3,4-dihydroxyphenyl)propionic acid; α-(monofluoromethyl)dopa; and α-(difluoromethyl)dopa.

20 180. The method of Claim 157 wherein said inhibitor compound is a dopa-decarboxylase inhibitor of the formula

25



wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, 5 amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro, alkylsulfonyloxy, carboxyalkoxy and formyl; 10 wherein each of R⁴⁹ and R⁵⁰ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, 15 alkynyl and

O
||
-CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy, aryloxy, aralkoxy, amino, monoalkylamino and dialkylamino; with the proviso that R⁴⁹ and R⁵⁰ cannot both be carboxyl at the same time, and with the further proviso that at least one of R⁴⁵ through R⁴⁸ is a primary or secondary amino group or a carboxyl group; or a pharmaceutically-acceptable salt thereof.

25 181. The method of Claim 180 wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, 30 monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl, alkynyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴⁹ and R⁵⁰ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, 35 aryl, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano,

amino, monoalkylamino, dialkylamino, carboxyalkyl and alkanoyl and

5 O
 ||
-CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy, phenoxy, benzyloxy, amino, monoalkylamino and dialkylamino.

182. The method of Claim 181 wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, benzyl, phenyl, alkoxy, benzyloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyl, carboxyalkyl, alkanoyl, cyanoamino, cyano, aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴⁹ and R⁵⁰ is independently selected from hydrido, alkyl, benzyl, phenyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, cyano, amino, monoalkylamino, dialkylamino, carboxyalkyl and alkanoyl and

20 O
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-CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy, amino and monoalkylamino.

183. The method of Claim 182 wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, alkoxy, haloalkyl, hydroxyalkyl, amino, monoalkylamino, carboxyl, carboxyalkyl aminomethyl, carboxyalkoxy and formyl; wherein each of R⁴⁹ and R⁵⁰ is independently selected from hydrido alkyl, amino, monoalkylamino, carboxyalkyl and

30 O
 ||
-CR⁵¹ wherein R⁵¹ is selected from hydroxy, alkoxy, amino and monoalkylamino.

184. The method of Claim 183 wherein each of R⁴⁵ through R⁴⁸ is independently selected from hydrido, hydroxy, alkyl, alkoxy and hydroxyalkyl; wherein each of R⁴⁹ and R⁵⁰ is independently selected 5 from alkyl, amino, monoalkylamino, and

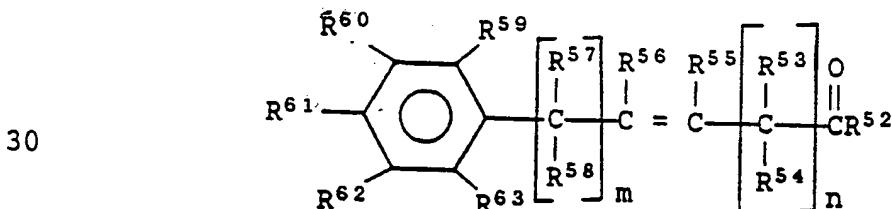
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-CR⁵¹ wherein R⁵¹ is selected from hydroxy, methoxy, ethoxy, propoxy, butoxy, amino, methylamino and 10 ethylamino.

185. The method of Claim 184 wherein said inhibitor compound is selected from endo-2-amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylic acid; 15 ethyl-endo-2-amino-1,2,3,4-tetrahydro-1,4-ethano-naphthalene-2-carboxylate hydrochloride; exo-2-amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylic acid; and 20 ethyl-exo-2-amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylate hydrochloride.

186. The method of Claim 157 wherein said inhibitor compound is a dopa-decarboxylase inhibitor selected from 2,3-dibromo-4,4-bis(4-ethylphenyl)-2-butenoic acid; 25 3-bromo-4-(4-methoxyphenyl)-4-oxo-2-butenoic acid; N-(5'-phosphopyridoxyl)-L-3,4-dihydroxyphenylalanine; N-(5'-phosphopyridoxyl)-L-m-aminotyrosine; D,L-β-(3,4-dihydroxyphenyl)lactate; D,L-β-(5-hydroxyindolyl-3)lactate; 30 2,4-dihydroxy-5-(1-oxo-2-propenyl)benzoic acid; 2,4-dimethoxy-5-[1-oxo-3-(2,3,4-trimethoxyphenyl-2-propenyl]benzoic acid; 2,4-dihydroxy-5-[1-oxo-3-(2-thienyl)-2-propenyl]benzoic acid;

- 2,4-dihydroxy-5-[3-(4-hydroxyphenyl)-1-oxo-2-propenyl] benzoic acid;
- 5-[3-(4-chlorophenyl)-1-oxo-2-propenyl]-2,4-dihydroxy benzoic acid;
- 5 2,4-dihydroxy-5-(1-oxo-3-phenyl-2-propenyl)benzoic acid;
- 2,4-dimethoxy-5-[1-oxo-3-(4-pyridinyl)-2-propenyl] benzoic acid;
- 10 5-[3-(3,4-dimethoxyphenyl)-1-oxo-2-propenyl]-2,4 dimethoxy benzoic acid;
- 2,4-dimethoxy-5-(1-oxo-3-phenyl-2-propenyl)benzoic acid;
- 5-[3-(2-furanyl)-1-oxo-2-propenyl]-2,4-dimethoxy benzoic acid;
- 15 2,4-dimethoxy-5-[1-oxo-3-(2-thienyl)-2-propenyl] benzoic acid;
- 2,4-dimethoxy-5-[3-(4-methoxyphenyl)-1-oxo-2-propenyl] benzoic acid;
- 20 5-[3-(4-chlorophenyl)-1-oxo-2-propenyl]-2,4-dimethoxy benzoic acid; and
- 5-[3-[4-(dimethylamino)phenyl]-1-oxo-2-propenyl]-2,4 dimethoxy benzoic acid.

187. The method of Claim 157 wherein said inhibitor compound is a dopa-decarboxylase inhibitor of the formula



wherein R⁵² is selected from hydrido, OR⁶⁴ and
 $\begin{array}{c} \text{R}^{65} \\ | \\ -\text{N}- \\ | \\ \text{R}^{66} \end{array}$, wherein R⁶⁴ is selected from

5 hydrido, alkyl, cycloalkyl, cycloalkylalkyl,
phenalkyl and phenyl, and wherein each of R⁶⁵ and R⁶⁶
is independently selected from hydrido, alkyl,
alkanoyl, amino, monoalkylamino, dialkylamino, phenyl
and phenalkyl; wherein each of R⁵³, R⁵⁴ and R⁵⁷
10 through R⁶³ is independently selected from hydrido,
hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl,
aryl, alkoxy carbonyl, hydroxyalkyl, halo, cyano,
amino, monoalkylamino, dialkylamino, carboxyl,
carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and
15 alkynyl; wherein each of R⁵⁵ and R⁵⁶ is independently
selected from hydrido, alkyl, cycloalkyl,
cycloalkylalkyl, aralkyl, aryl, alkoxyalkyl,
haloalkyl, hydroxyalkyl and carboxyalkyl; wherein
each of m and n is a number independently selected
20 from zero through six, inclusive; or a
pharmaceutically-acceptable salt thereof.

188. The method of Claim 187 wherein R⁵²
is OR⁶⁴ wherein R⁶⁴ is selected from hydrido, alkyl,
cycloalkyl, cycloalkylalkyl, benzyl and phenyl;
25 wherein each of R⁵³, R⁵⁴ and R⁵⁷ through R⁶³ is
independently selected from hydrido, alkyl,
cycloalkyl, hydroxy, alkoxy, benzyl and phenyl;
wherein each of R⁵⁵ and R⁵⁶ is independently selected
30 from hydrido, alkyl, cycloalkyl, benzyl and phenyl;
wherein each of m and n is a number independently
selected from zero through three, inclusive.

189. The method of Claim 188 wherein R⁵²
is OR⁶⁴ wherein R⁶⁴ is selected from hydrido and
lower alkyl; wherein each of R⁵³ through R⁵⁸ is
35 hydrido; wherein each of R⁵⁹ through R⁶³ is

independently selected from hydrido, alkyl, hydroxy and alkoxy, with the proviso that two of the R⁵⁹ through R⁶³ substituents are hydroxy; wherein each of m and n is a number independently selected from zero through two, inclusive.

190. The method of Claim 189 wherein said inhibitor compound is 3-(3,4-dihydroxyphenyl)-2-propenoic acid.

191. The method of Claim 180 wherein said dopa-decarboxylase inhibitor is a compound selected from amino-haloalkyl-hydroxyphenyl propionic acids; alpha-halomethyl-phenylalanine derivatives; and indole-substituted halomethylamino acids.

192. The method of Claim 180 wherein said dopa-decarboxylase inhibitor is a compound selected from isoflavone extracts from fungi and streptomyces; sulfinyl substituted dopa and tyrosine derivatives; hydroxycoumarin derivatives; 1-benzylcyclobutenyl alkyl carbamate derivatives; aryl/thienyl-hydroxylamine derivatives; and β-2-substituted-cyclohepta-pyrrol-8-1H-on-7-yl alanine derivatives.

193. The method of Claim 157 wherein said dopamine-β-hydroxylase inhibitor compound is of the formula



wherein B is selected from an ethylenic moiety, an acetylenic moiety and an ethylenic or acetylenic moiety substituted with one or more radicals selected

from substituted or unsubstituted alkyl, aryl and heteroaryl; wherein each of R⁶⁷ and R⁶⁸ is independently selected from hydrido and alkyl; wherein R⁶⁹ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is a number selected from one through five.

10 194. The method of Claim 193 wherein B is an ethylenic or an acetylenic moiety substituted with an aryl or heteroaryl radical; and wherein n is a number from one through three.

15 195. The method of Claim 193 wherein B is an ethylenic or acetylenic moiety incorporating carbon atoms in the beta- and gamma-positions relative to the nitrogen atom; and wherein n is one.

20 196. The method of Claim 195 wherein said ethylenic or acetylenic moiety is substituted at the gamma carbon with an aryl or heteroaryl radical.

25 197. The method of Claim 196 wherein said aryl radical is selected from phenyl, 2-thiophene, 3-thiophene, 2-furanyl, 3-furanyl, oxazolyl, thiazolyl and isoxazolyl, any one of which radicals may be substituted with one or more groups selected from halo, hydroxyl, alkyl, haloalkyl, cyano, alkoxy, alkoxyalkyl and cycloalkyl.

30 198. The method of Claim 197 wherein said aryl radical is selected from phenyl, hydroxyphenyl, 2-thiophene and 2-furanyl; and wherein each of R⁶⁷, R⁶⁸ and R⁶⁹ is hydrido.

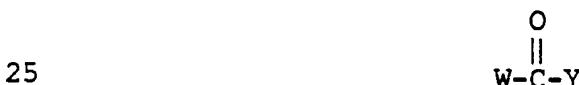
199. The method of Claim 198 wherein said inhibitor compound is selected from the group consisting of

- 3-amino-2-(2'-thienyl)propene;
- 5 3-amino-2-(2'-thienyl)butene;
- 3-(N-methylamino)-2-(2'-thienyl)propene;
- 3-amino-2-(3'-thienyl)propene;
- 3-amino-2-(2'-furanyl)propene;
- 3-amino-2-(3'-furanyl)propene;
- 10 1-phenyl-3-aminopropyne; and
- 3-amino-2-phenylpropene.

200. The method of Claim 198 wherein said inhibitor compound is selected from the group consisting of

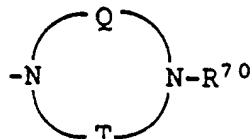
- 15 (\pm)4-amino-3-phenyl-1-butyne;
- (\pm)4-amino-3-(3'-hydroxyphenyl)-1-butyne;
- (\pm)4-amino-3-(4'-hydroxyphenyl)-1-butyne;
- (\pm)4-amino-3-phenyl-1-butene;
- (\pm)4-amino-3-(3'-hydroxyphenyl)-1-butene; and
- 20 (\pm)4-amino-3-(4'-hydroxyphenyl)-1-butene.

201. The method of Claim 157 wherein said inhibitor compound is of the formula



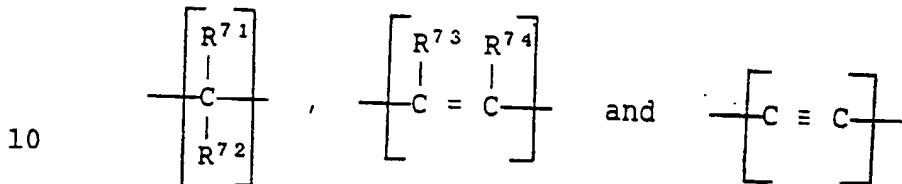
wherein W is selected from alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl; wherein Y is selected from

30



wherein R⁷⁰ is selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl,

aralkyl, aryl, alkanoyl, alkoxy carbonyl, carboxyl, amino, cyano amino, mono alkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein each of Q and T is one or more groups independently selected from

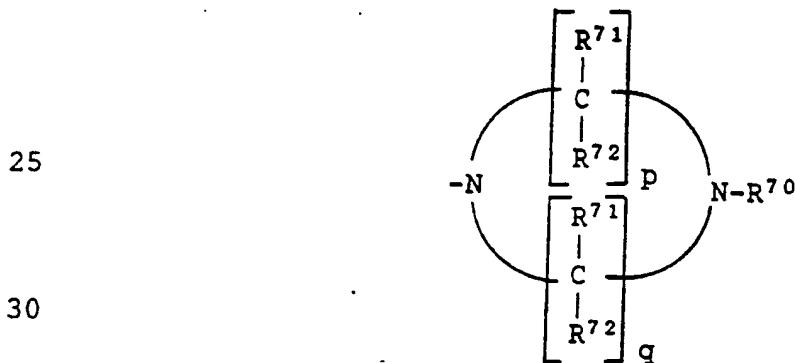


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wherein each of R⁷¹ through R⁷⁴ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, mono alkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; or a pharmaceutically-acceptable salt thereof.

20

202. The method of Claim 201 wherein W is heteroaryl and Y is



30

wherein R⁷⁰ is selected from hydrido, alkyl, amino, mono alkylamino, dialkylamino, phenyl and phenalkyl; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, mono alkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and

wherein each of p and q is a number independently selected from one through six, inclusive.

203. The method of Claim 202 wherein R⁷⁰ is selected from hydrido, alkyl, amino and
5 monoalkylamino; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive.

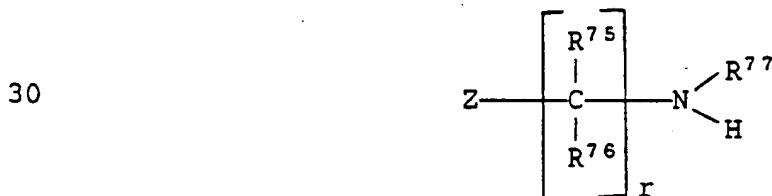
10 204. The method of Claim 203 wherein R⁷⁰ is selected from hydrido, alkyl and amino; wherein each of R⁷¹ and R⁷² is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected
15 from the numbers two and three.

205. The method of Claim 204 wherein R⁷⁰ is hydrido; wherein each of R⁷¹ and R⁷² is hydrido; and wherein each of p and q is two.

206. The method of Claim 157 wherein said
20 inhibitor compound is of the formula

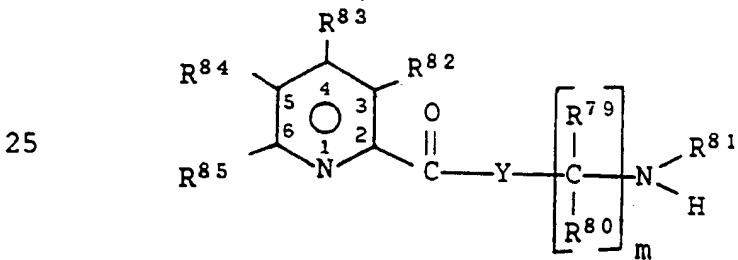


25 wherein E is selected from alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl; wherein F is selected from



wherein Z is selected from O, S and N-R⁷⁸; wherein each of R⁷⁵ and R⁷⁶ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, 5 alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, minoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R⁷⁵ and R⁷⁶ may form oxo or thio; wherein r is a number selected from zero 10 through six, inclusive; wherein each of R⁷⁷ and R⁷⁸ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, 15 dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; or a pharmaceutically-acceptable salt thereof.

207. The method of Claim 157 wherein said dopamine-β-hydroxylase inhibitor compound is of the formula



30 wherein each of R⁸² through R⁸⁵ is independently selected from hydrido, alkyl, haloalkyl, mercapto, alkylthio, cyano, alkoxy, alkoxyalkyl and cycloalkyl; wherein Y is selected from oxygen atom and sulfur atom; wherein each of R⁷⁹ and R⁸⁰ is independently selected from hydrido and alkyl; wherein R⁷⁹ is 35 selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl,

aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein m is a number from one through six; or a 5 pharmaceutically-acceptable salt thereof.

208. The method of Claim 207 wherein each of R⁸² through R⁸⁵ is independently selected from hydrido, alkyl and haloalkyl; wherein Y is selected from oxygen atom or nitrogen atom; wherein each of R⁷⁹, 10 R⁸⁰ and R⁸¹ is independently hydrido and alkyl; and wherein m is a number selected from one through four, inclusive.

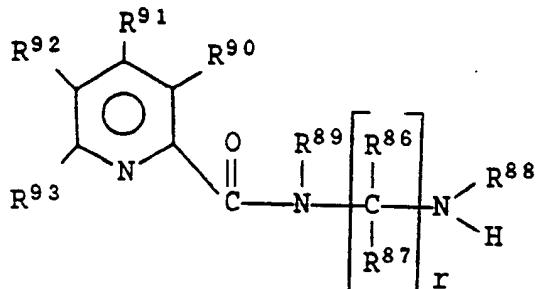
209. The method of Claim 208 wherein said inhibitor compound is selected from 15 aminomethyl-5-n-butylthiopicolinate; aminomethyl-5-n-butylpicolinate; 2'-aminoethyl-5-n-butylthiopicolinate; 2'-aminoethyl-5-n-butylpicolinate; (2'-amino-1',1'-dimethyl)ethyl-5-n-butylthiopicolinate; 20 (2'-amino-1',1'-dimethyl)ethyl-5-n-butylpicolinate; (2'-amino-1'-methyl)ethyl-5-n-butylthiopicolinate; (2'-amino-1'-methyl)ethyl-5-n-butylpicolinate; 3'-aminopropyl-5-n-butylthiopicolinate; 3'-aminopropyl-5-n-butylpicolinate; 25 (2'-amino-2'-methyl)propyl-5-n-butylthiopicolinate; (2'-amino-2'-methyl)propyl-5-n-butylpicolinate; (3'-amino-1',1'-dimethyl)propyl-5-n-butylthiopicolinate; (3'-amino-1',1'-dimethyl)propyl-5-n-butylpicolinate; (3'-amino-2',2'-dimethyl)propyl-5-n-butylthiopicolinate; 30 (3'-amino-2',2'-dimethyl)propyl-5-n-butylpicolinate; 2'-aminopropyl-5-n-butylthiopicolinate; 2'-aminopropyl-5-n-butylpicolinate; 4'-aminobutyl-5-n-butylthiopicolinate; 4'-amino-3'-methylbutyl-5-n-butylthiopicolinate;

(3'-amino-3'-methyl)butyl-5-n-butylthiopicolinate; and
(3'-amino-3'-methyl)butyl-5-n-butylpicolinate.

210. The method of Claim 201 wherein said inhibitor compound is of the formula

5

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wherein each of R⁸⁶, R⁸⁷ and R⁹⁰ through R⁹³ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl; wherein R⁸⁶ and R⁸⁷ together may form oxo or thio; wherein r is a number selected from zero through six, inclusive; wherein each of R⁸⁸ and R⁸⁹ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl, aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino, cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl..

211. The method of Claim 210 wherein each of R⁸⁶, R⁸⁷ and R⁹⁰ through R⁹³ is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; wherein r is a number selected from zero through four, inclusive; wherein

each of R⁸⁸ and R⁸⁹ is independently selected from hydrido, alkyl, amino, monoalkylamino, dialkylamino, phenyl and phenalkyl.

212. The method of Claim 211 wherein each of
 5 R⁸⁶, R⁸⁷ and R⁹⁰ through R⁹³ is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein r is a number selected from zero through three, inclusive; and wherein each of R⁸⁸ and R⁸⁹ is selected from
 10 hydrido, alkyl, amino and monoalkylamino.

213. The method of Claim 212 wherein each of
 R⁹⁰ through R⁹³ is independently selected from hydrido and alkyl; wherein each of R⁸⁶ and R⁸⁷ is hydrido; wherein r is selected from zero, one and
 15 two; wherein R⁸⁸ is selected from hydrido, alkyl and amino; and wherein R⁸⁹ is selected from hydrido and alkyl.

214. The method of Claim 213 wherein said inhibitor compound is 5-n-butylpicolinic acid hydrazide.

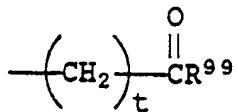
20 215. The method of Claim 157 wherein said dopamine-β-hydroxylase inhibitor compound is of the formula



wherein each of R⁹⁴ through R⁹⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, aryloxy, alkoxy, alkylthio, aralkoxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino,

dialkylamino, amido, alkylamido, hydroxyamino,
 carboxyl, carboxyalkyl, alkanoyl, alkenyl,
 cycloalkenyl, alkynyl, cyanoamino, carboxyl,
 thiocarbamoyl, aminomethyl, alkylsulfanamido, nitro,
 5 alkylsulfonyloxy, formoyl and alkoxycarbonyl; with
 the proviso that at least one of R⁹⁴ through R⁹⁸ is

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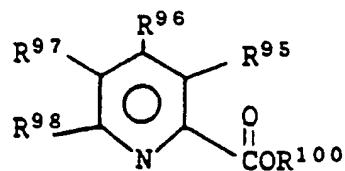
wherein R⁹⁹ is selected from hydrido, alkyl, hydroxy,
 alkoxy, alkylthio, phenyl, phenoxy, benzyl, benzyloxy,

15

-OR¹⁰⁰ and -N^{R¹⁰¹}_{R¹⁰²}, wherein R¹⁰⁰ is selected from
 hydrido, alkyl, cycloalkyl, cycloalkylalkyl, phenyl
 and benzyl and each of R¹⁰¹ and R¹⁰² is independently
 selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl,
 haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl,
 20 aryl, alkanoyl, alkoxycarbonyl, carboxyl, amino,
 cyanoamino, monoalkylamino, dialkylamino, alkylsulfinyl,
 alkylsulfonyl, arylsulfinyl and arylsulfonyl; wherein
 t is a number selected from zero through four,
 inclusive; or a pharmaceutically-acceptable salt
 25 thereof.

216: The method of Claim 215 wherein said
 inhibitor compound is of the formula

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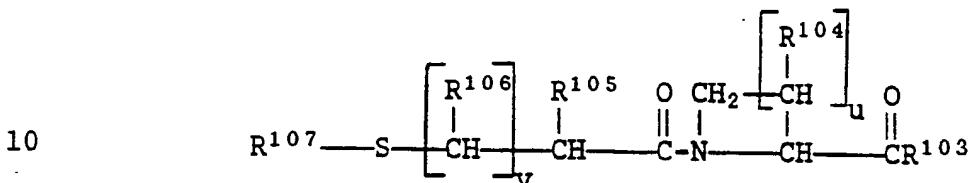


wherein each of R⁹⁵ through R⁹⁸ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, phenyl, benzyl, alkoxy, phenoxy, benzyloxy, alkoxyalkyl, hydroxyalkyl, halo, cyano, amino, 5 monoalkylamino, dialkylamino, amido, alkylamido, hydroxyamino, carboxyl, carboxyalkyl, alkanoyl, cyanoamino, carboxyl, thiocarbamoyl, aminomethyl, nitro, formoyl, formyl and alkoxycarbonyl; and wherein R¹⁰⁰ is selected from hydrido, alkyl, phenyl 10 and benzyl.

217. The method of Claim 216 wherein said inhibitor compound is selected from
5-n-butylicolic acid;
5-ethylpicolinic acid;
15 picolinic acid;
5-nitropicolinic acid;
5-aminopicolinic acid;
5-N-acetylaminopicolinic acid;
5-N-propionylaminopicolinic acid;
20 5-N-hydroxyaminopicolinic acid;
5-iodopicolinic acid;
5-bromopicolinic acid;
5-chloropicolinic acid;
5-hydroxypicolinic acid
25 5-methoxypicolinic acid;
5-N-propoxypicolinic acid;
5-N-butoxypicolinic acid;
5-cyanopicolinic acid;
5-carboxylicolic acid;
30 5-n-butyl-4-nitropicolinic acid;
5-n-butyl-4-methoxypicolinic acid;
5-n-butyl-4-ethoxypicolinic acid;
5-n-butyl-4-aminopicolinic acid;
5-n-butyl-4-hydroxyaminopicolinic acid; and
35 5-n-butyl-4-methylpicolinic acid.

218. The method of Claim 217 wherein said inhibitor compound is 5-n-butylpicolinic acid.

219. The method of Claim 157 wherein said dopamine- β -hydroxylase inhibitor compound is of the formula



wherein R¹⁰³ is hydrido, hydroxy, alkyl, amino and alkoxy; wherein R¹⁰⁴ is selected from hydrido, hydroxy and alkyl; wherein each of R¹⁰⁵ and R¹⁰⁶ is independently selected from hydrido, alkyl and phenalkyl; wherein R¹⁰⁷ is selected from hydrido and

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20
25

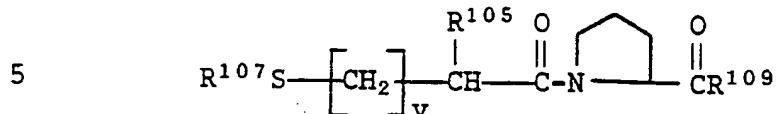
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||
R¹⁰⁸C- with R¹⁰⁸ selected from alkyl, phenyl and phenalkyl; wherein u is a number from one to three, inclusive; and wherein v is a number from zero to two, inclusive; or a pharmaceutically-acceptable salt thereof.

220. The method of Claim 219 wherein R¹⁰³ is selected from hydroxy and lower alkoxy; wherein R¹⁰⁴ is hydrido; wherein R¹⁰⁵ is selected from hydrido and lower alkyl; wherein R¹⁰⁶ is hydrido; wherein R¹⁰⁷ is selected from hydrido and

30
35

O
||
R¹⁰⁸C- with R¹⁰⁸ selected from lower alkyl and phenyl; wherein u is two; and wherein v is a number from zero to two, inclusive.

221. The method of Claim 220 wherein said inhibitor compound is of the formula



wherein R^{109} is selected from hydroxy and lower alkyl; wherein R^{105} is selected from hydrido and lower alkyl; wherein R^{107} is selected from hydrido and

10 $\begin{matrix} \text{O} \\ \parallel \\ \text{R}^{108}\text{C}- \end{math}$ with R^{108} selected from lower alkyl and phenyl and v is a number from zero to two, inclusive.

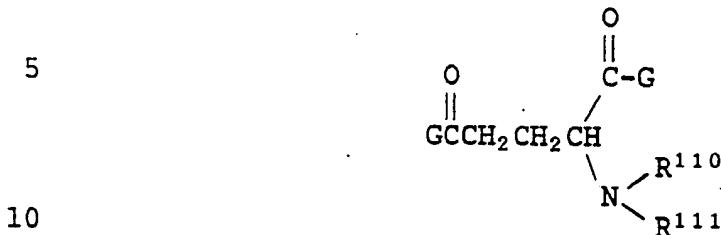
15 222. The method of Claim 221 wherein R^{109} is hydroxy; wherein R^{105} is hydrido or methyl; wherein R^{107} is hydrido or acetyl; and wherein n is a number from zero to two, inclusive.

20 223. The method of Claim 222 wherein said inhibitor compound is 1-(3-mercaptop-2-methyl-1-oxopropyl)-L-proline.

224. The method of Claim 156 wherein said precursor compound providing the second residue has a reactable acid moiety.

25 225. The method of Claim 224 wherein said second residue precursor compound of said conjugate is

selected from a class of glutamic acid derivatives of the formula



wherein each of R^{110} and R^{111} may be independently selected from hydrido, alkylcarbonyl, alkoxy carbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-\text{OR}^{112}$, 15 $-\text{SR}^{113}$ and $>\text{NR}^{114}$ with each of R^{112} , R^{113} and R^{114} independently selected from hydrido and alkyl; with the proviso that said glutamic acid is selected such that formation of the cleavable amide bond occurs at the gamma-position carbon of said gamma-glutamic acid residue.

226. The method of Claim 225 wherein said second residue precursor compound of said conjugate is the glutamic acid derivative gamma-glutamic acid.

227. The method of Claim 226 wherein R^{110} is hydrido, and R^{111} is selected from

25

$$\begin{array}{c}
 \text{O} \\
 || \\
 -\text{CR}^{115}
 \end{array}$$

wherein R^{115} is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, 30 tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

228. The method of Claim 227 wherein said second residue precursor compound of said conjugate is the glutamic acid derivative is N-acetyl- γ -glutamic acid.

229. The method of Claim 157 wherein said conjugate comprises a first residue provided by a dopamine- β -hydroxylase inhibitor compound and a second residue provided by a gamma glutamic acid derivative.

5 230. The method of Claim 229 wherein said dopamine- β -hydroxylase inhibitor is fusaric acid or fusaric acid hydrazide and said gamma glutamic acid derivative is N-acetyl- γ -glutamic acid.

10 231. The method of Claim 230 wherein said conjugate is N-acetyl- γ -glutamyl fusaric acid hydrazide.

232. The method of Claim 155 wherein said hypertensive-related disorder is chronic hypertension.

15 233. The method of Claim 155 wherein said sodium-retaining disorder is congestive heart failure, or cirrhosis, or nephrosis.

Acute In Vivo Effects of Vehicle and
Example #3 Conjugate

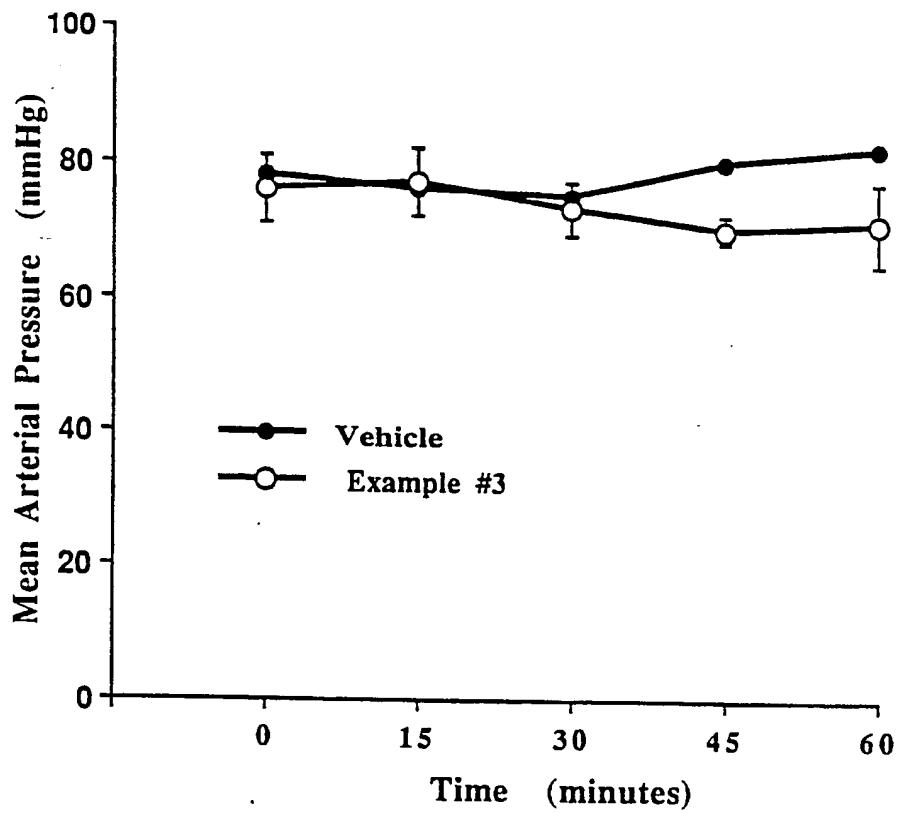


Figure 1

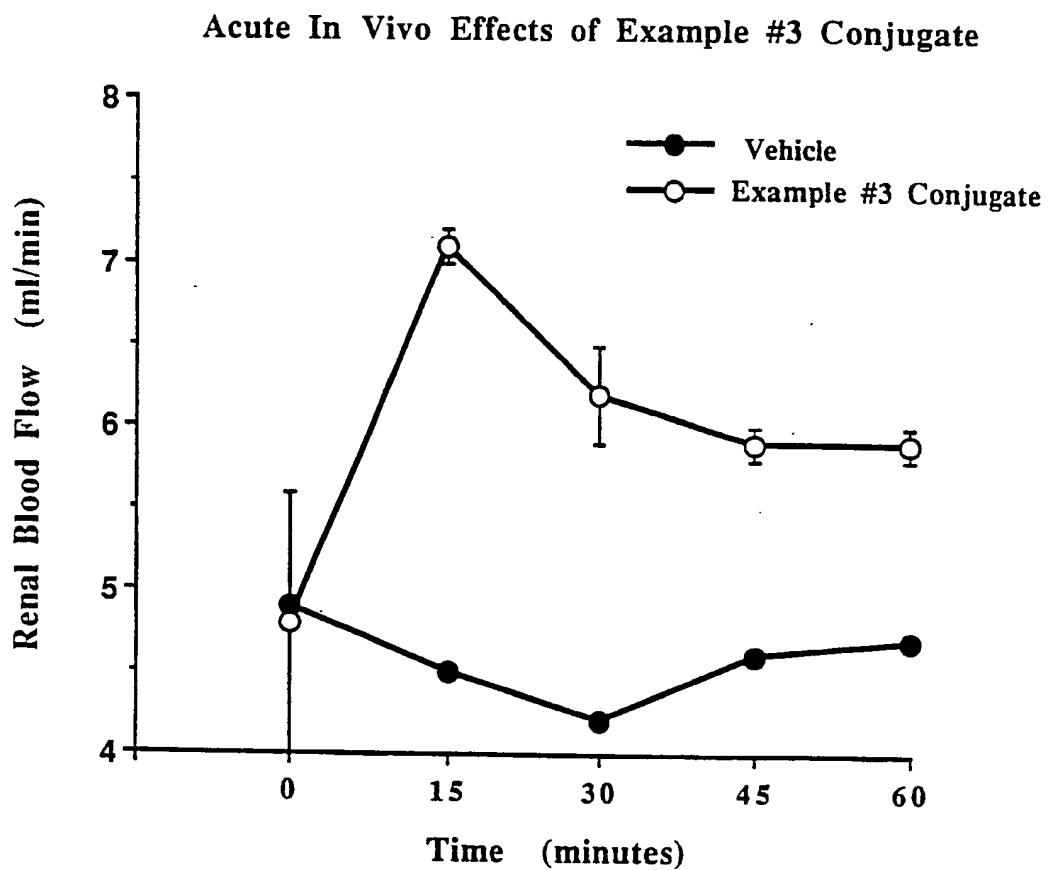
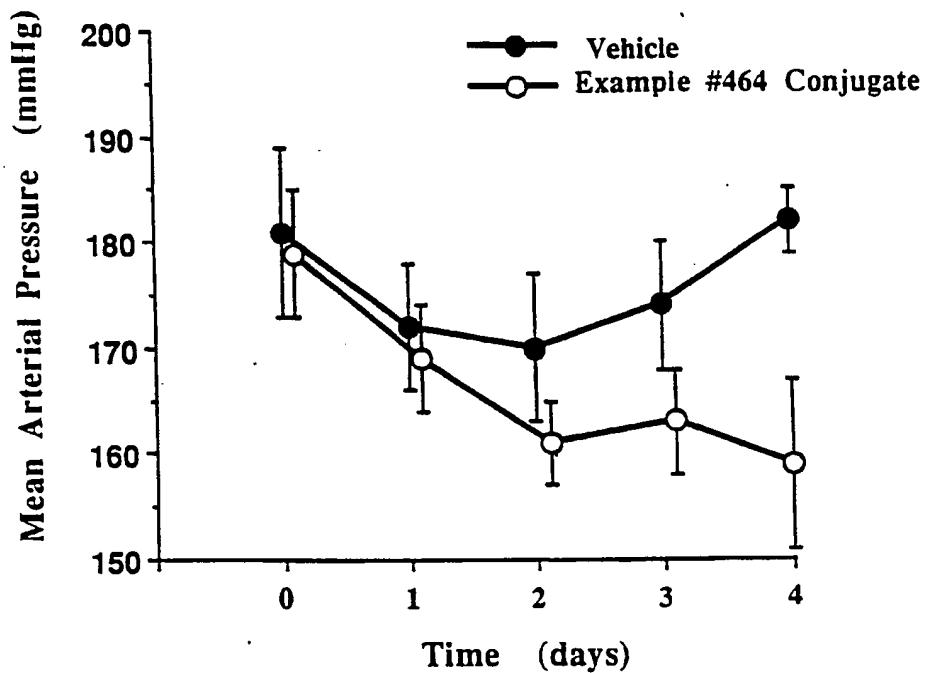


Figure 2

Chronic Infusion of Example #464 Conjugate**Figure 3**

Formation of Fusaric Acid From Example #859
Conjugate by Rat Kidney Homogenate

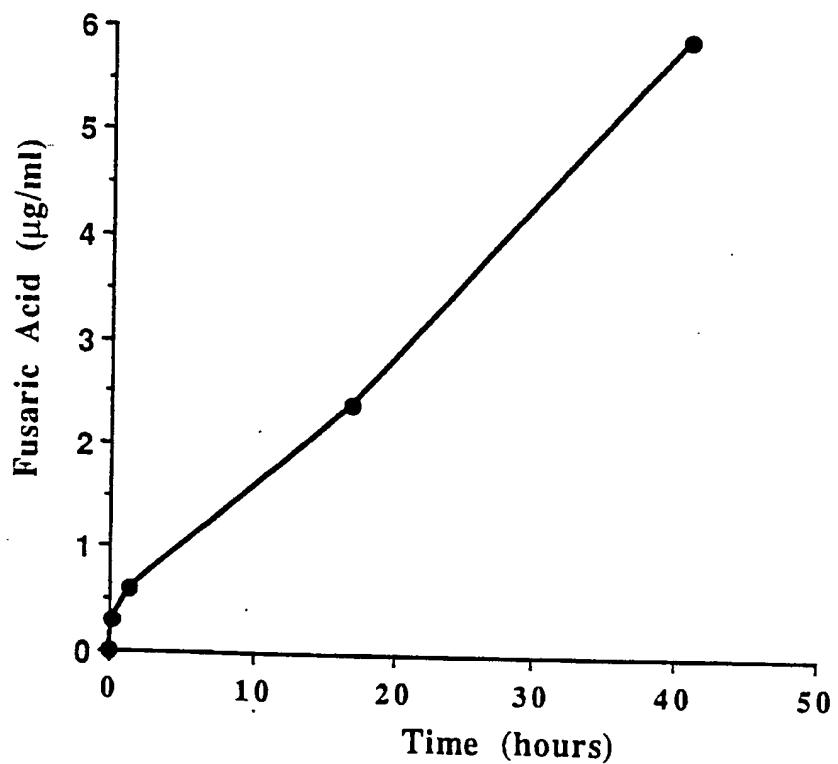


Figure 4

Enzymatic Formation of Fusaric Acid From Example #859 Conjugate

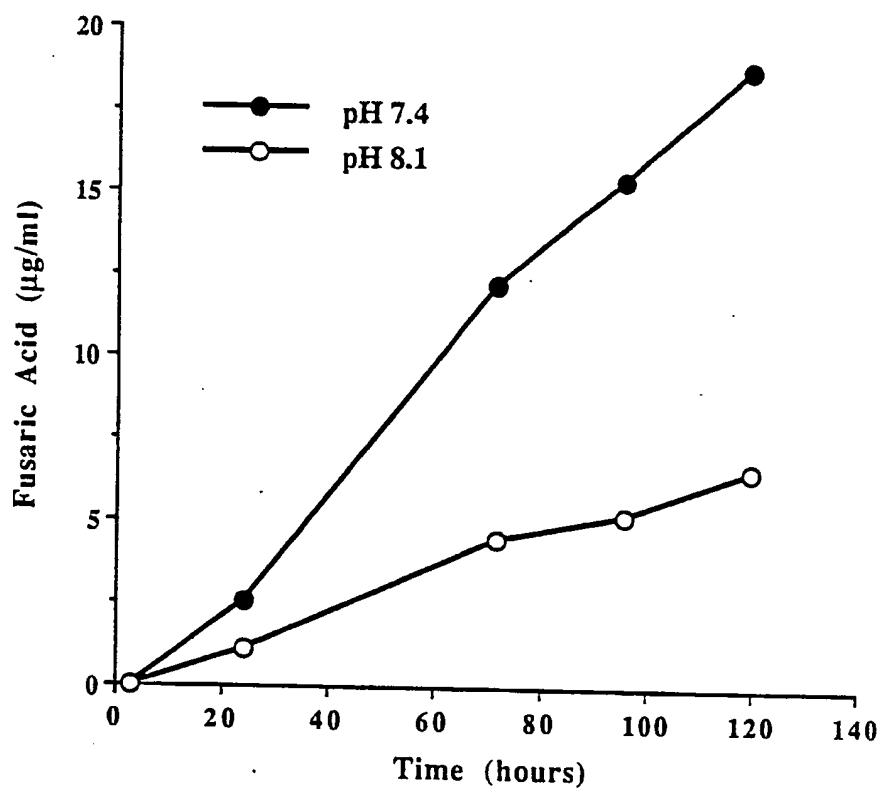


Figure 5

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Effect of Fusaric Acid and Example #859 Conjugate
on Dopamine- β -Hydroxylase Activity In Vitro

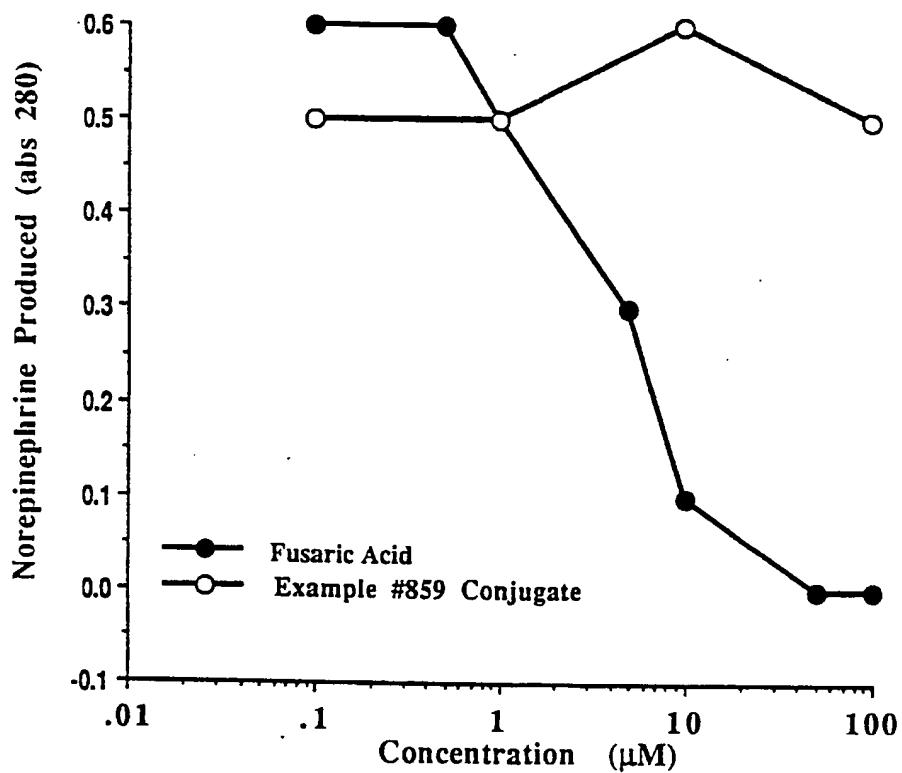


Figure 6

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Dopamine- β -Hydroxylase Inhibition by
Example #859 Conjugate and Related Compounds

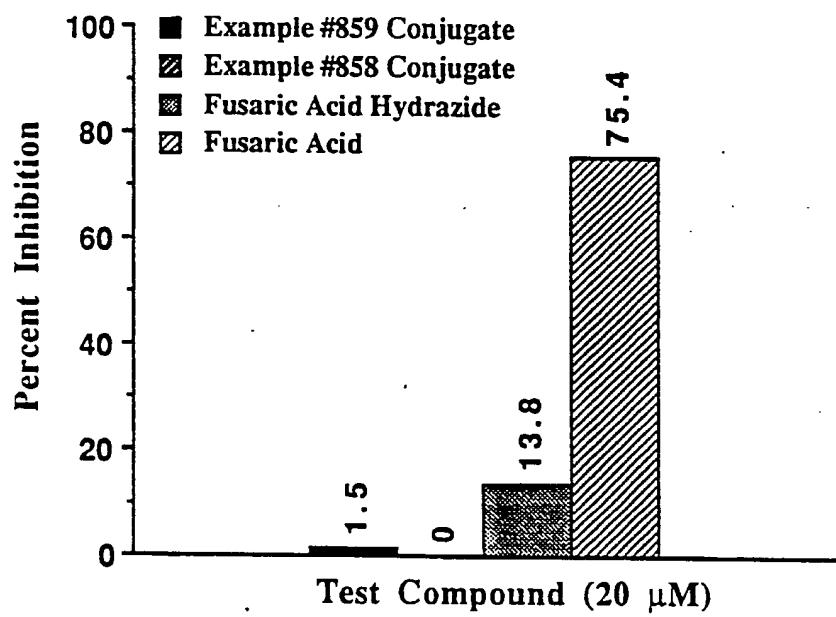


Figure 7

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Acute In Vivo Effects of Fusaric Acid or
Example #859 Conjugate on Mean Arterial Pressure

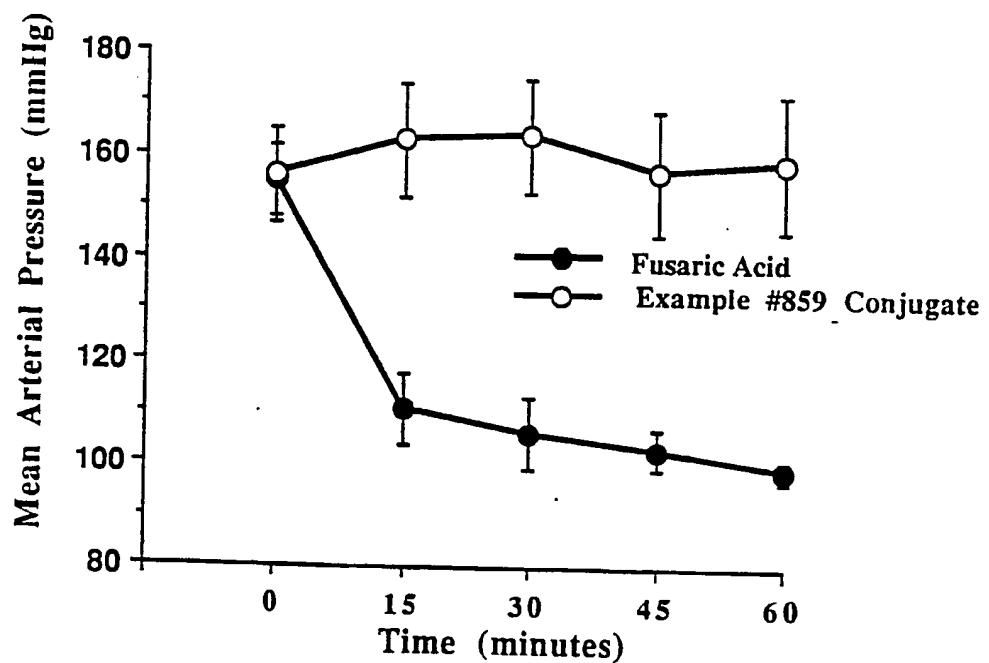


Figure 8

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Acute In Vivo Effects of Fusaric Acid and
Example #859 Conjugate on Renal Blood Flow

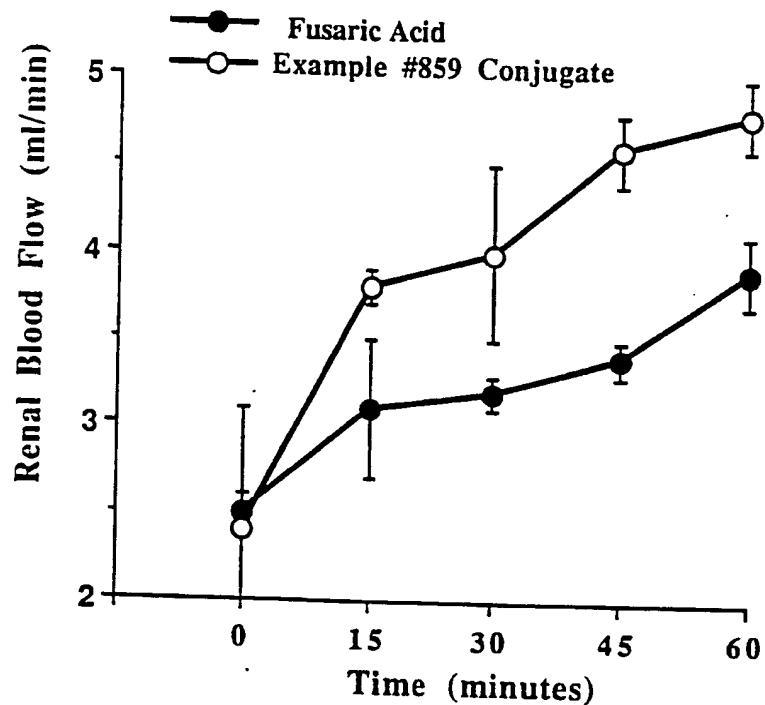


Figure 9

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Chronic In Vivo Effects of Saline, Fusaric Acid and Example #859 Conjugate

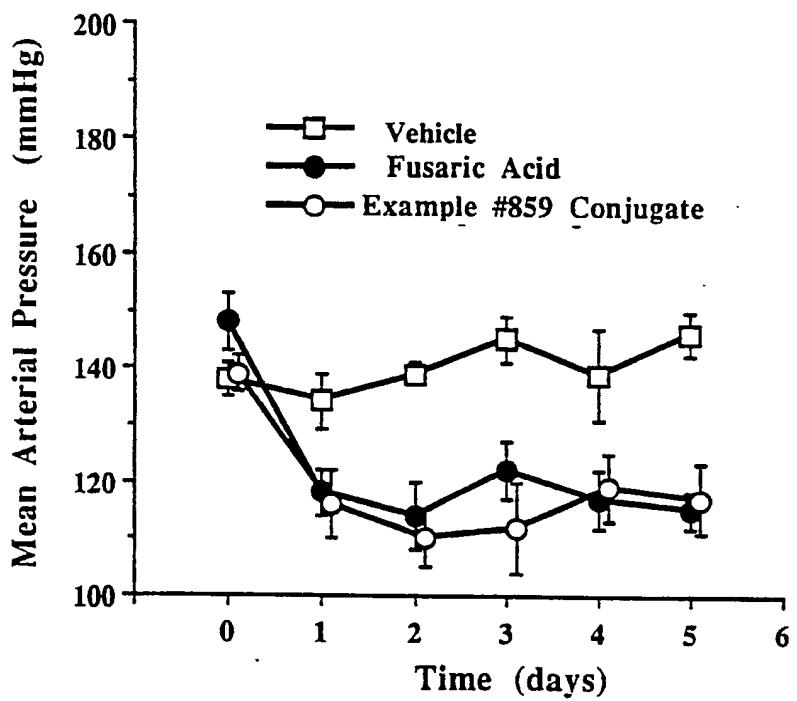


Figure 10

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Chronic Infusion of Example #863 Conjugate

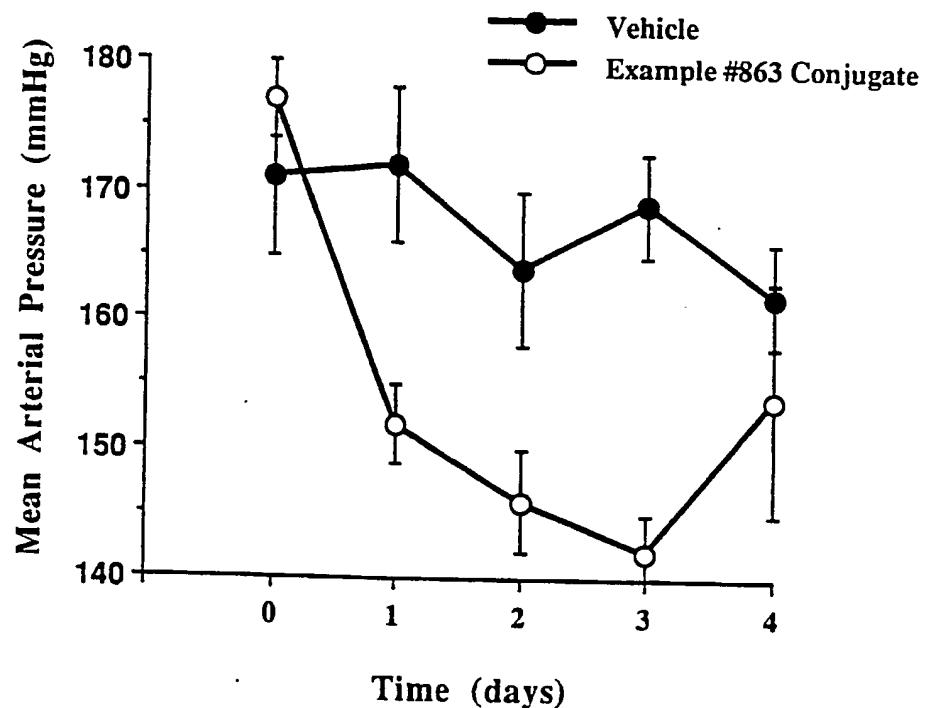


Figure 11

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Heart Norepinephrine Levels Following
5 Day Infusion of Vehicle, Fusaric Acid,
and Example #859 Conjugate

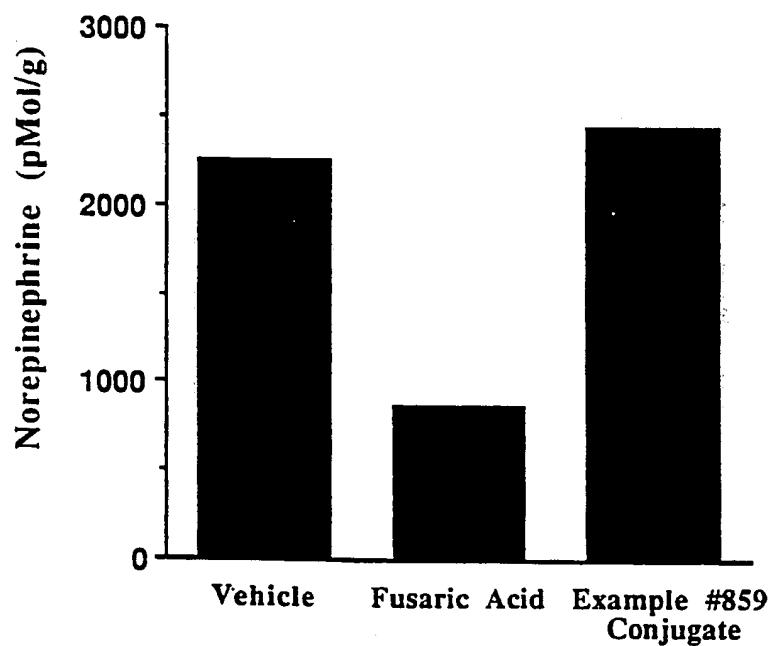


Figure 12

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Kidney Norepinephrine Levels Following
5 Day Infusion of Vehicle, Fusaric Acid,
and Example #859 Conjugate

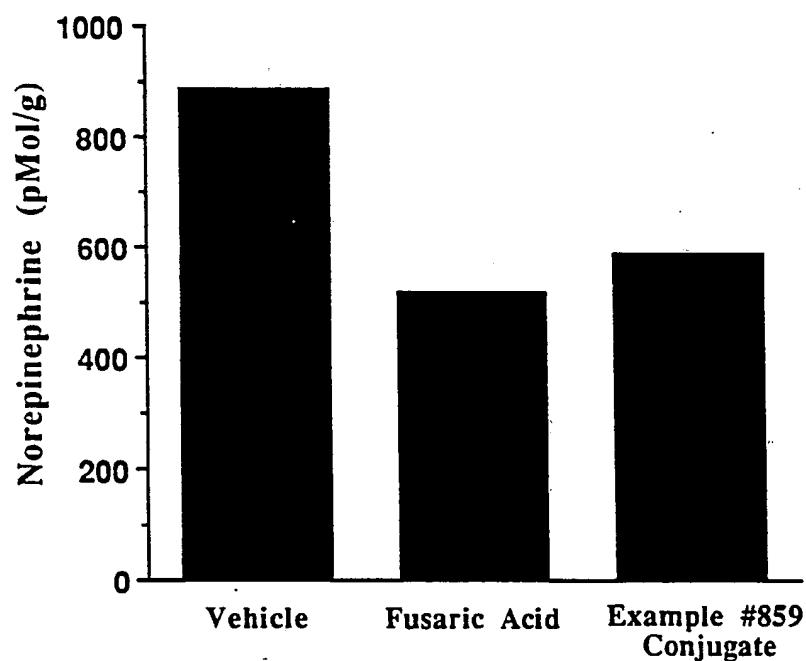


Figure 13

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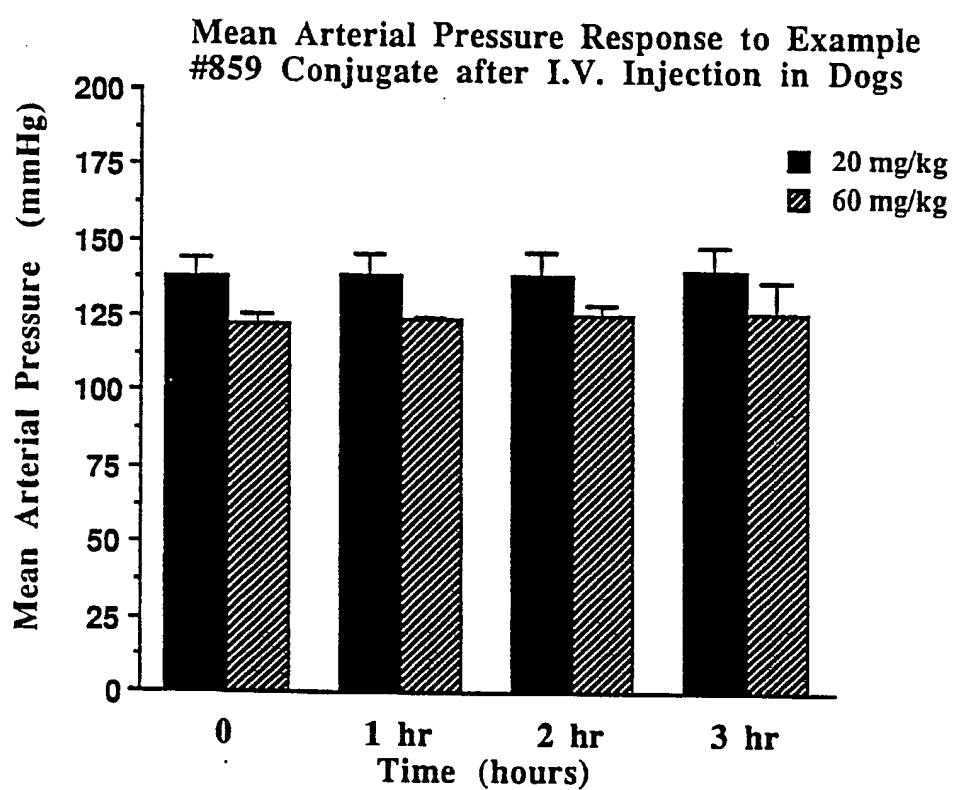


Figure 14

Renal Blood Flow Response to Example #859
Conjugate After I.V. Injection in Dogs

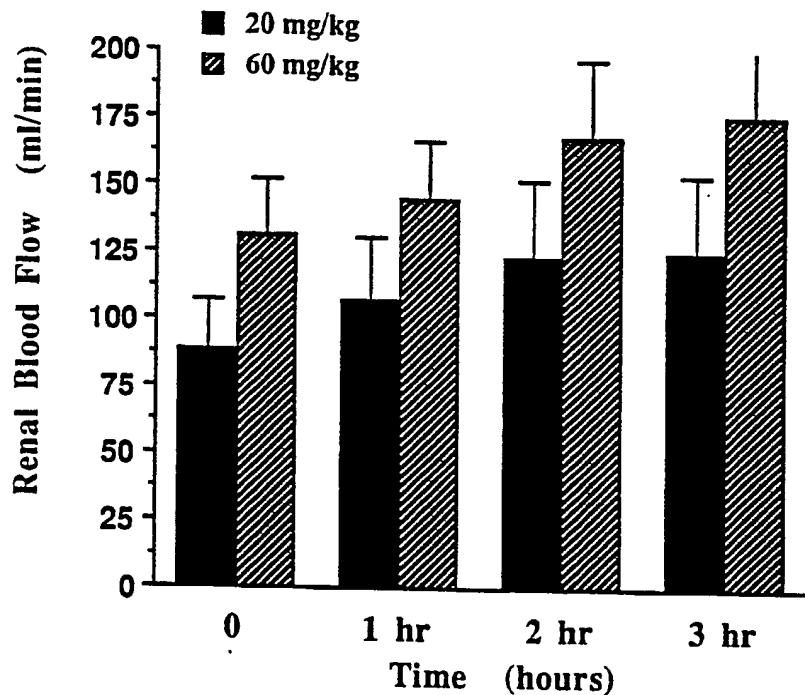


Figure 15

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US90/04168

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ¹⁾		I.P.C. (5)
According to International Patent Classification (IPC) or to both National Classification and/or PCT	A61K 31/12, 13, 16, 33, 34, 35, 38, 40, 41, 46, 47, 50, 55, 395, 405, 415, 495, 535	
B07C 71/00, 211/00, 237/00, 255/00, C07D — continue next page		

II. FIELDS SEARCHED

Classification System		Minimum Documentation Searched
		Classification Symbols
US 514	183,210,218,230,5,247,249,311,353,361,396,415,423,438,443,451,461,613,659,663,678,680	
US 540	203,470,553	
<i>continue next page</i>		
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ²⁾		

III. DOCUMENTS CONSIDERED TO BE RELEVANT³⁾

Category ⁴⁾	Citation of Document, ⁵⁾ with indication, where appropriate, of the relevant passages ⁶⁾	Relevant to Claim No. ⁷⁾
X	DT, A, 2,450,161 Apr 24, 1975 p. Jones, J. Kyndl, W. Carroll	1-3,70-74, 78-80, 147-151, 155-157
X	N, Clin. and Exper.— Theory and Practice, A9(546),977-986, 1987 "Dopamine, the kidney and essential hypertension studies with GLUDOPA", M.R. Lee	1-3,70-74,78-80 147-151,155-157 32-36,110-113,186-192 47-51,172-179
X	N, Br. J. Clin. Pharmac., 25 195-201, 1988 R.F. Jeffrey, T.M. McDonald, K. Morwick, M.R. Lee "The effect of carbidopa and indometacin on the renal response to L-glutamyl-L-dopa in normal man"	1-3, 70-74, 78-80 147-151, 155-157 32-36,110-113, 186-192 47-51, 172-179
X	N, Chemical Abstract, volume 87, No. 19, p.180, 1977 abst. No. 147351v (Columbus Ohio, USA)Okada, K.,Kawase, M., "Mass spectral differentiation of L- and D-linkages in glutamyl oligopeptides and its application for structure elucidation of naturally occurring peptides" Chem. Pharm. Bull 25(7) 1497-508, 1977	4-25,78-80,81-102 32-36,47-51

* Special categories of cited documents:¹⁾

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the International Filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search ⁸⁾	Date of Mailing of this International Search Report ⁹⁾
06 DECEMBER 1990	23 JAN 1991
International Searching Authority ¹⁰⁾ ISA / US	Signature of Authorized Officer ¹¹⁾ <i>Chia-Chen CELIA CHANG</i>

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET**I. Subject matter classification - continue**

IPC CODE 205/12, 209/04, 213/00, 215/12, 233/54, 237/00, 241/36, 243/00, 245/00, 265/36
265/14, 295/00 307/02, 315/00, 333/20

II. Field of search continue

US 544/105,224,349	US 558/303
US 546/176,267	US 564/123,453,463
US 548/127,335,469,538	US 568/306,326
US 549/58,74,426,491	

V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. Claim numbers ..., because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim numbers ..., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claim numbers ..., because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

see attachment pages.

Lack of unity of invention has been found to exist because each group on the attached grouping schedule represents structurally different, independent and distinct invention.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. As all searchable claims could be searched without justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- The additional search fees were accompanied by applicant's protest.
- No protest accompanied the payment of additional search fees.

The following groups of invention have been identified:

- I. Claims 53-64, 130-141, drawn to dopamine -B-hydroxylase inhibitor and composition when the inhibitor has a six member heteroring with one nitrogen, classified in classes 546, 514, subclasses 267, 353.
- II. Claims 65-69, 142-146, drawn to dopamine -B-hydroxylase inhibitor and composition when the inhibitor has a five member heteroring with one nitrogen, classified in classes 548, 514, subclasses 538, 423.
- III. Claims 47-52, 124-129, drawn to dopamine -B-hydroxylase inhibitor and composition when the inhibitor has a four member heteroring with two nitrogens, classified in classes 540, 514, subclasses 203, 210.
- IV. Claims 47-52, 124-129, drawn to dopamine -B-hydroxylase inhibitor and composition when the inhibitor has a five member heteroring with two nitrogens, classified in classes 548, 514, subclasses 335, 396.
- V. Claims 47-52, 124-129, drawn to dopamine -B-hydroxylase inhibitor and composition when the inhibitor has a six member heteroring with two nitrogens, classified in classes 544, 514, subclasses 224, 247.
- VI. Claims 47-52, 124-129, drawn to dopamine -B-hydroxylase inhibitor and composition when the inhibitor has a seven member heteroring with two nitrogens, classified in classes 540, 514, subclasses 553, 218.
- VII. Claims 47-52, 124-129, drawn to dopamine -B-hydroxylase inhibitor and composition when the inhibitor has a eight member heteroring with two nitrogens, classified in classes 540, 514, subclasses 470, 183.

- VIII. Claims 39-46, 116-123, drawn to dopamine - β -hydroxylase inhibitor and composition when the inhibitors are amines with non heterocyclic substituents, classified in classes 564, 514, subclasses 123, 613.
- IX. Claims 4-17 and 81-94, drawn to tyrosin hydroxylase inhibitors and compositions when A and R^a are nonheterocyclic substituted phenyls, classified in Class 568, 514, subclass 306, 678.
- X. Claims 4-17 and 81-94 drawn to tyrosin hydroxylase inhibitors and compositions when A and R^a are imidazole, classified in Class 568, 514, subclass 335, 395.
- XI. Claims 4-17, 81-94, drawn to tyrosin hydroxylase inhibitor and composition when A or R^a is indole, classified in classes 568, 514 subclasses 469, 415.
- XII. Claims 14-17, 81-94, drawn to tyrosin hydroxylase inhibitor and composition when A and R^a are nonheterocyclic polycycles, classified in Classes 568, 514, subclasses 326, 680.
- XIII. Claims 18-38, 95-102, drawn to dopa-decarboxylase inhibitor and composition when the inhibitor is of the formula as claim 95, classified in classes 564, 558, 514, subclasses 463, 303, 663.
- XIV. Claims 18-38, 110-115, drawn to dopa-decarboxylase inhibitor and composition when the inhibitor is of the formula as claim 110, classified in classes 568, 514, subclasses 306, 678.
- XV. Claims 18-38, 103-109, drawn to dopa-decarboxylase inhibitor and composition when the inhibitor is of the formula as claim 103, classified in classes 558, 564, 514, subclasses 303, 453, 659.
- XVI. Claims 158-171, drawn to method of treating chronic hypertension, congestive heart failure, nephrosis, cirrhosis, sodium retaining disorder using a tyrosin hydroxylase inhibitor.

- XVII. Claims 172-192 drawn to method of treating chronic hypertension, congestive heart failure, nephrosis, cirrhosis, sodium retaining disorder using a dopa-decarboxylase inhibitor.
- XVIII. Claims 193-233 drawn to method of treating chronic hypertension, congestive heart failure, nephrosis, cirrhosis, sodium retaining disorder using a dopamine -B- hydroxylase inhibitor.

The following claims are generic to all the compounds and methods: claims 1-3, 70-80, 147-157, 233.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ^{1a} with indication, where appropriate, of the relevant passages ^{1b}	Relevant to Claim No. 11
X	N, Chemical Abstracts, volume 88, No. 3, 1978, page 683, Abst. No. 23368g (Columbus, Ohio, U.S.A.) A. Yasutake, H. Aoyagi, N. Iamida, "Studies on separation of amino acids and related compounds VIII. Preparative separation of isomeric L- α - β -phenylalanine methyl esters and related dipeptide esters by ion-exchanger chromatography" Bull. Chem. Soc. Jpn. <u>50</u> (9) 2413-16, 1977 (Eng)	4-25, 78-80, 81-102 32-36, 47-51
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category*	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
X	US, A, 4,296,119, October 20, 1981 Wurtman et al.	4-25, 78-102, 155-179 47-51, 81-102, 158-171
X	US, A, 4,299,838, Nov. 10, 1981 Duriach et al.	4-25, 78-102, 155-179 47-51, 158-171
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